(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 July 2002 (11.07.2002)

PCT

(10) International Publication Number
WO 02/054085 A1

(51) International Patent Classification[7]: G01N 35/02

(21) International Application Number: PCT/US02/00064

(22) International Filing Date: 4 January 2002 (04.01.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/259,758 4 January 2001 (04.01.2001) US

(71) Applicant *(for all designated States except US)*: **CHEMCODES, INC.** [US/US]; Suite G, Commercial Park West, 2300 Englert Drive, Durham, NC 27713 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **FREDERICK, Erik, D.** [US/US]; 4508 Bracada Drive, Durham, NC 27705 (US). **EICHENBAUM, Gary, M.** [US/US]; 1332 Southpoint Crossing Drive, Durham, NC 27713 (US). **POLYAKOV, Valery, R.** [US/US]; 11 Clover Drive, Chapel Hill, NC 27514 (US). **GEYSEN, Hendrik, M.** [US/US]; 2884 Mechum Drive, Charlottesville, VA 22901 (US).

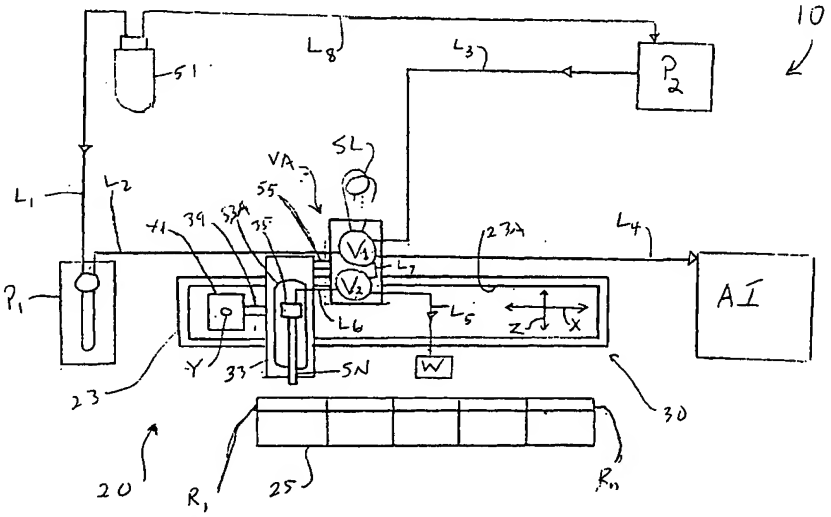
(74) Agent: **JENKINS, Richard, E.**; Suite 1400, University Tower, 3100 Tower Boulevard, Durham, NC 27707 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: APPARATUS, METHOD AND COMPUTER PROGRAM PRODUCT FOR AUTOMATED HIGH-THROUGHPUT SAMPLING AND DATA ACQUISITION



(57) Abstract: In a method, apparatus and computer program product for acquiring data from a sample, a sample or at least an initial portion thereof is transferred into an analytical instrument and the analytical instrument acquires data from the sample. While the analytical instrument is acquiring data, one or more properties of the sample are measured or the status of the system or instrumentation is considered. A determination is made as to whether the sample of the associated system or instrumentation meets one or more decision criteria (273) based on the one or more properties measured or on the status information obtained. A valve assembly (60) is_also provided that is adjustable to at least three modes operation, a sample injection/needle rinse mode, a sample loop load/instrument flush mode, and a sample loop flush/instrument flush mode.

WO 02/054085 A1

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Description

APPARATUS, METHOD AND COMPUTER PROGRAM PRODUCT FOR AUTOMATED HIGH-THROUGHPUT SAMPLING AND DATA ACQUISITION

Related Applications

This application claims the benefit of U.S. Provisional Patent Application Serial No. 60/259,758, filed January 4, 2001, the disclosure of which is incorporated herein by reference in its entirety.

Technical Field

The present invention relates to apparatus, methods and computer program products for implementing and controlling improved high-throughput sampling and data acquisition. More particularly, the present invention relates to valve configurations and computer software for improving such sampling and data acquisition.

Background Art

Drug discovery typically involves the analysis of a large number of samples in order to acquire useful data. The time period required for performing a multiple-sample analysis is thus an important criterion, as it determines the cost of the analysis as well as the sample throughput. Advances in automated engineering and computing have contributed significantly to the automation of many of the procedural steps required in carrying out sample analyses, such as sample preparation, introduction, measurement, interpretation, and cleanup. Many types of microprocessor-controlled automated devices are now commercially available for use in sampling and data acquisition. Examples of automated liquid handling devices are disclosed in U.S. Patent Nos. 4,422,151 and 5,988,236. Accordingly, much progress has been made toward increasing sample throughput, as well as improving procedural reproducibility, reducing the level of human skill required, reducing the degree of human error, and reducing the amount of tedious

human intervention required. It is well recognized by persons skilled in the art, however, that the pursuit of increased throughput is ongoing. Therefore, there remains a need for further improvements in devices and procedures employed in sampling and data acquisition.

Disclosure of the Invention

The present invention in one aspect achieves increased throughput by integrating sample delivery and data acquisition/analysis systems. In one embodiment, the present invention provides a computer software-controlled, robotic autosampling system for the rapid injection and flushing of samples into an analytical instrument such as, for example, a mass spectrometer. In a preferred embodiment, the system comprises a valve assembly, a sample injection loop, appropriate tubing and pumps, a sampling probe such as an injection needle mounted on a robotic apparatus, and the analytical instrument. The software consists of instrument controlling objects that function in a synchronous or asynchronous mode. The software controls all aspects of the sampling and data acquisition processes implemented by the system, including sample take-up, sample injection, sampling needle rinsing, sample loop flushing, and sample injection flow rate. The system provided by the invention enables an increase in sample throughput over conventional single-valve injection port-based systems.

The invention provides a novel valve assembly or system that is integrated with software to allow rapid sampling of multiple samples with minimal inter-sample delay and signal carryover. Preferably, the valve assembly is mounted to the robotic apparatus in close proximity to the sampling needle, so that the valve assembly is mounted within approximately 30 cm of any sample site of the system, and to limit dead volume to, in the non-limiting case of micro-sample delivery, less than approximately 35 µL. Preferably, a sample loop is connected to the valve assembly.

In one embodiment, the valve assembly comprises a pair of multiport valves (each including, for example, six ports). Each valve is adjustable to at least two positions. By altering the combination of respective positions of the

two valves, at least three positional modes can be realized by the valve assembly. These modes are referred to herein as the sample injection/needle rinse mode, the sample loop load/instrument flush mode, and the sample loop flush/instrument flush mode. At each mode, at least two fluid flow paths can be simultaneously active. In the sample injection/needle rinse mode, a sample injection flow path and a sampling needle rinsing flow path are defined. This mode is utilized to inject a sample contained in the sample loop, while simultaneously allowing the needle to be rinsed using an appropriate pump such as a syringe pump. In the sample loop load/instrument flush mode, a sampling loop loading flow path and an instrument flushing flow path are defined. This mode allows the sample loop to be loaded from the needle using the syringe pump, while simultaneously maintaining a continuous flow of solvent to the analytical instrument. In the sample loop flush/instrument flush mode, a sample loop flushing flow path as well as the instrument flushing flow path are defined. This position allows sample injection to be interrupted without having to flush the entire sample into the analytical instrument. At an arbitrary time, the valve assembly can be switched to this position, and the remaining sample in the sample loop is diverted and flushed to waste and clean solvent is introduced into the analytical instrument at a constant rate. Preferably, at all times (i.e., during each mode), the flow of a fluid (either a sample solution or clean solvent) to the analytical instrument is maintained. In another embodiment, the valve assembly comprises a single multiport valve that is adjustable to at least three positions for realization of the three functional modes.

The valve assembly and associated autosampling system are provided in accordance with the present invention to address the needs of increased sample throughput into an analytical instrument. In practice, the invention in at least one preferred embodiment satisfies the following conditions:

a) Flow to the analytical instrument must not be interrupted between samples.

b) The injection needle or probe employed by the system must be able to be rinsed during the injection of a sample.

c) The system must be able to make a decision, based on predetermined parameters or algorithms, to dynamically abort a sample by flushing the sample to a waste line instead of through the analytical device.

In one embodiment of the invention, a sample is taken up into an injection loop and pumped into the analytical instrument through the valve system. Based on a data-driven, software-controlled decision, the sample is either flushed to waste or sampled to completion. Additionally, placement of the valve system in close proximity to the sampling needle results in increased throughput by minimizing the time required for a sample to travel between the autosampling system and the analytical instrument, as well as a reduction in deadspace.

According to one method of the invention, sample acquisition is performed by transferring a sample or at least an initial portion thereof into an analytical instrument. The analytical instrument acquires data from the sample. While the analytical instrument is acquiring data, one or more properties of the sample are measured or the status of the system or instrumentation is considered. A determination is made as to whether the sample or the associated system or instrumentation meets one or more decision criteria based on the one or more properties measured or on the status information obtained. In response to determining that the sample, system, or instrumentation has failed to meet any of the one or more decision criteria, the analytical instrument is caused to cease acquiring data from the sample or initial portion thereof. In response to determining that the sample, system, or instrumentation has met all of the one or more decision criteria, an additional portion of the sample is transferred into the analytical instrument and the analytical instrument acquires data from the additional portion.

In accordance with this method, when the decision criteria is not met, a remaining portion of the sample can be prevented from being injected into the analytical instrument. The remaining portion can be discarded or diverted away from the analytical instrument. The remaining sample can also be transferred to a suitable apparatus, such as another analytical modality.

According to another method of the invention for acquiring data from a sample. A sample is loaded into a sample reservoir such as a sample loop from a sample conduit that can include a sampling needle and associated plumbing. While the sample is being loaded an injection conduit is flushed. The injection conduit can include an analytical instrument and/or plumbing necessary for transferring the sample into the analytical instrument. At least a portion of the sample is injecting through the injection conduit into an analytical instrument. While the sample is being injected, the sample conduit is flushed. The sample reservoir is also flushed. While the sample reservoir is being flushed, the injection conduit is flushed. These steps can be repeating for additional samples.

According to another aspect of the present invention, the methods summarized hereinabove and described in more detail hereinbelow can be implemented by a computer program product comprising computer-executable instructions embodied in a computer-readable medium.

According to another embodiment of the present invention, a valve assembly for use in sample data acquisition comprises a sample loop and a valve. The valve comprises an aspiration/dispensing port, a sampling port, a waste port, a pump-side port, and an instrument-side port. The valve is selectively adjustable to at least first, second and third positions. The first position defines a sample injection flow path and a sampling probe flushing path, the second position defines a sample loop loading flow path and an instrument flushing flow path, and the third position defines a sample loop flushing flow path.

In a preferred embodiment, the sample injection flow path is directed from the pump-side injection port, through the sample loop, and to the instrument-side injection port. The sampling probe flushing path is directed from the aspiration/dispensing port to the sampling port. The sample loop loading flow path is directed from the sampling port to the sample loop. The instrument flushing flow path is directed from the pump-side injection port to the instrument-side injection port. The sample loop flushing flow path is directed

from the aspiration/dispensing port, through the sample loop, and to the waste port.

According to yet another embodiment of the present invention, the valve assembly comprises a valve structure and a movable valve body. The valve structure comprises the aspiration/dispensing port, the sampling port, the waste port, the pump-side port, and the instrument-side port. The valve body comprises a plurality of internal fluid passages selectively communicating with one or more of the ports of the valve structure at the first, second and third positions.

The present invention provides embodiments of the valve assembly in dual-valve rotary, single-valve linear, and single-valve rotary configurations.

According to still another embodiment of the present invention, a sample analysis system comprises a robotic assembly, a sampling probe movably mounted to the robotic assembly, a sample loop, and a valve assembly mounted to the robotic assembly. The valve assembly comprises an aspiration/dispensing port, a sampling port, a waste port, a pump-side port, and an instrument-side port. The valve assembly is selectively adjustable to at least first, second and third positions. The first position defines a sample injection flow path and a sampling probe flushing path, the second position defines a sample loop loading flow path and an instrument flushing flow path, and the third position defines a sample loop flushing flow path. Preferably, a reversible pump such as a syringe pump fluidly communicates with the aspiration/dispensing port, a waste receptacle fluidly communicates with the waste port, an instrument pump fluidly communicates with the pump-side port, and an analytical instrument such as a mass spectrometer fluidly communicating with the instrument-side port.

It is therefore an object of the present invention to provide means for improved automated high-throughput sampling and data acquisition, in the form of an apparatus, method, and/or computer program product.

It is another object of the present invention to provide a valve assembly that is adjustable to several different positions in order to realize several operational modes by which throughput can be increased.

It is yet another object of the present invention to provide computer software for controlling such a valve assembly.

It is still another object of the present invention to provide computer software for implementing a data-driven decisional process by which a sample can be rejected or diverted prior to completion of data acquisition of that sample.

Some of the objects of the invention having been stated hereinabove, other objects will become evident as the description proceeds when taken in connection with the accompanying drawings as best described hereinbelow.

Brief Description of the Drawings

Figure 1 is a schematic view of an automated sampling and data acquisition system provided in accordance with the present invention;

Figure 2 is an exploded perspective view of a conventional multiport valve suitable for use in certain embodiments of the invention;

Figure 3A is a schematic diagram of a valve assembly provided in accordance with one embodiment of the present invention and positioned at a sample injection/needle rinsing mode;

Figure 3B is a schematic view of the valve assembly illustrated in Figure 3A and positioned at a sample loop load/instrument flush mode;

Figure 3C is a schematic view of the valve assembly illustrated in Figures 3A and 3B and positioned at a sample loop flush/instrument flush mode;

Figure 4 is a partially cutaway cross-sectional view of a valve assembly provided in accordance with another embodiment of the present invention;

Figure 5A is a schematic diagram of the valve assembly illustrated in Figure 4 and positioned at a sample injection/needle rinsing mode;

Figure 5B is a schematic diagram of the valve assembly illustrated in Figure 4 and positioned at a sample loop load/instrument flush mode;

Figure 5C is a schematic diagram of the valve assembly illustrated in Figure 4 and positioned at a sample loop flush/instrument flush mode;

Figure 6 is a cutaway cross-sectional view of a valve assembly provided in accordance with yet another embodiment of the present invention;

Figure 7A is a top plan view of an upper valve structure of the valve assembly illustrated in Figure 6;

Figure 7B is a bottom plan view of a lower valve structure of the valve assembly illustrated in Figure 6;

Figure 7C is a perspective view of a valve body of the valve assembly illustrated in Figure 6;

Figure 8A is a schematic diagram of the valve assembly illustrated in Figure 6 and positioned at a sample injection/needle rinsing mode;

Figure 8B is a schematic diagram of the valve assembly illustrated in Figure 6 and positioned at a sample loop load/instrument flush mode;

Figure 8C is a schematic diagram of the valve assembly illustrated in Figure 6 and positioned at a sample loop flush/instrument flush mode;

Figure 9 is a schematic diagram illustrating an exemplary operational control environment for the system illustrated in Figure 1;

Figures 10A and 10B are block diagrams illustrating a sampling and data acquisition process carried out by the present invention;

Figure 11 is a block diagram illustrating a data-driven decisional process executed by computer software in accordance with the present invention;

Figure 12 is a plot of intensity versus time illustrating the rapid data acquisition of multiple samples in accordance with the present invention; and

Figure 13 is a plot of intensity versus time illustrating the throughput performance achieved by the present invention in comparison to the performance achieved by a conventional sampling and data acquisition system.

Detailed Description of the Invention

In general, the term "communicate" (e.g., a first component "communicates with" or "is in communication with" a second component) is used herein to indicate a structural, functional, mechanical, optical, or fluidic relationship between two or more components or elements. As such, the fact that one component is said to communicate with a second component is not

intended to exclude the possibility that additional components may be present between, and/or operatively associated or engaged with, the first and second components.

As used herein, the terms "valve assembly" and "valve system" are taken to mean a valve unit that contains a single valve or manifold structure or a plurality of valves or manifold structures.

As used herein, the terms "rinsing" and "flushing" are used interchangeably to mean replacing a plug or volume of fluid with clean solvent and/or cleaning the inner walls of a liquid conduit by carrying away residual contaminants.

Referring now to the schematic view of Figure 1, an automated sampling and data acquisition system, generally designated **10**, is illustrated in accordance with the invention. Sampling system **10** comprises a liquid handling apparatus, generally designated **20**; a valve assembly **VA**; one or more solvent reservoirs **51**; a high-pressure pump unit P_2; an analytical instrument **AI**; and an electronic control unit or computer **100** with computer software **112** (see Figure 9).

Liquid handling apparatus **20** is generally employed to perform sample preparation and liquid handling procedures, including the sequential injections of samples into analytical instrument **AI**. Preferably, the operations of liquid handling apparatus **20** are programmable by means of written, executable software instructions for these purposes. By way of example, liquid handling apparatus **20** comprises a main structural frame (a portion of which is designated **23**) on which various operative components are supported. Preferably attached to or supported by main frame **23** is a rack assembly **25** on which a variety of different types of racks or plates R_1 - R_n can be removably mounted. As appreciated by persons skilled in the art, racks R_1 - R_n are usually constructed of aluminum, polypropylene, or quartz, depending on the particular application or sample composition contemplated. Racks R_1 - R_n can be plates that include respective arrays of wells for containing sample solutions, or can include an array of holes for holding vials, test tubes, cuvettes or other types of vessels that in turn contain sample solutions. For example, each rack R_1 - R_n

could constitute a conventional 96-well microtitre plate, thereby enabling liquid handling apparatus **20** to process a large number of different samples.

It will be understood that liquid handling apparatus **20** could be an originally constructed apparatus, or could be provided as or adapted from a commercially available apparatus. One example of a suitable commercially available apparatus is a Gilson™ Model 215 Liquid Handler™ apparatus available from Gilson, Inc., Middleton, Wisconsin. Such an apparatus, as well as other similar liquid handling apparatuses, conventionally provides an injection port for direct injection of samples into an HPLC unit or an injection module for injection of samples into a mass spectrometry unit. The standard injection port or module, however, is not required in the present invention.

Also attached to main frame **23** is a robotic assembly, generally designated **30**, that is designed for electronically controlled, programmable three-axis movement. Robotic assembly **30** includes a sample aspiration and dispensing device, which preferably is provided as a sampling probe or needle **SN**. While conventional needles typically have a 0.03-inch bore, it is preferable that sampling needle **SN** used in the present invention have a 0.015-inch bore to further minimize deadspace and reduce the volume of the sample in the sample vessels required for filling a sample loop or other suitable sample reservoir. The tip of sampling needle **SN** can be sharpened if desired to enable penetration through the septum of a sample-holding container that is sealed in such manner. Sampling needle **SN** is linked to a vertical arm **33** of robotic assembly **30** by a suitable needle mounting unit or carriage unit **35**. Sampling needle **SN** and its carriage unit **35** slide along a vertical track **33A** of vertical arm **33** along a vertical direction indicated by vertical axis **Z**. Vertical arm **33** is linked through a suitable linkage **39** to a horizontal arm **41**. Vertical arm **33** and its linkage **39** slide along a horizontal track (not shown) along a horizontal direction running into and out of the sheet of Figure 1, as indicated by the point of horizontal axis **Y**. Horizontal arm **41** is linked to main frame **23** and slides along a horizontal track **23A** along a horizontal direction indicated by horizontal axis **X**. It thus can be seen that robotic assembly **30** can be programmed to move sampling needle **SN** to and from various sites of liquid handling

apparatus **20**, including the various wells or vessels disposed on racks R_1 - R_n as well as a rinsing station or waste receptacle **W** ordinarily integrally provided in some form with liquid handling apparatus **20**.

Liquid handling apparatus **20** further includes a pump P_1, which can be integrated with liquid handling apparatus **20** or provided as a separate module. Preferably, pump P_1 is a syringe pump or other conventionally designed pump that is capable of reversible or two-way flow (i.e., for both aspiration and dispensing), and to which inlet and outlet liquid transfer lines L_1 and L_2, respectively, are connected. Liquid transfer lines L_1 and L_2, as well as other liquid transfer lines utilized in the practice of the invention, are usually constructed of PTFE tubing or a similarly chemically inert and flexible material. Inlet liquid transfer line L_1 communicates with one or more solvent reservoirs **51**. Outlet liquid transfer line L_2 conventionally communicates directly with sampling needle **SN**, but in the present invention communicates with valve assembly **VA** as described in more detail hereinbelow.

Valve assembly **VA** is configured to enable the advantageous methods of the present invention as described in more detail hereinbelow. In one embodiment, valve assembly **VA** comprises two multiport valves V_1 and V_2 as specifically shown in Figure 1. Alternatively, valve assembly **VA** comprises a single multiport valve in accordance with other embodiments of the invention described hereinbelow. Each valve V_1 and V_2 provided by valve assembly **VA** can be of conventional design.

Referring to Figure 2, a typical valve, generally designated **60**, includes a rotary valve body **62** and a stationary structure such as a disk **64**. Valve body **62** contains a network of internal passages **66A**, **66B** and **66C**, and disk **64** has a plurality of ports **68A – 68F** that communicate with one or more of internal passages **66A -- 66C**. Transfer tubing lines (not shown in Figure 2) are connected to one or more of ports **68A – 68F** to enable fluid communication between valve **60** and the fluid circuit in which valve **60** operates along desired flow paths. Other ports **68A – 68F** may be plugged to prevent siphoning and entry of air into the system. Valve body **62** can be rotated in an indexing fashion by a stepper motor **70** and suitable coupling and transmission means to

re-align ports **68A – 68F** with at least some of internal passages **66A -- 66C** and thus switch or alter the course or courses of one or more flow paths associated with the fluid circuit. One example of a multiport valve that is suitable for use as a valve of valve assembly **VA** is the Rheodyne™ Model 7010 valve incorporated into the Gilson™ Model 819 Injection Module™ apparatus available from Gilson, Inc., Middleton, Wisconsin.

Figure 1 illustrates a preferred embodiment of the fluid circuit arrangement associated with sampling system **10** in accordance with the invention. As described hereinabove, syringe pump P_1 communicates with solvent reservoir **51** through liquid transfer line L_1, and with valve V_1 through liquid transfer line L_2. Valve V_1 communicates with high-pressure pump P_2 through a liquid transfer line L_3, and with analytical instrument **AI** through a liquid transfer line L_4. Valve V_1 also includes a sample loop **SL**, the use and operation of which are generally known in the art, or some other type of sample reservoir suitable for containing a precise volume of a liquid-phase containing substance such as a solvent or a sample carried by a mobile phase or dissolved in a solvent. Valve V_2 communicates with waste receptacle **W** through a liquid transfer line L_5, and with sampling needle **SN** through a liquid transfer line L_6. Finally, valves V_1 and V_2 communicate with each other through a fluid transfer line L_7. Valve assembly **VA** is mounted directly to robotic assembly **30** so as to minimize the length of fluid passages and hence the total dead volume. Preferably, valve assembly **VA** is mounted to vertical arm **33** of robotic assembly **30** through a suitable mounting bracket or bracket assembly **55**. In the present embodiment, the dead volume is defined by the volume of sampling needle **SN**, the volume of liquid transfer line L_6, the volume of liquid transfer line L_7 and the internal volumes of V_1 and V_2. In the case where micro-sampling is contemplated, the total dead volume is less than approximately 35 µL, and valves V_1 and V_2 are disposed within approximately 30 cm of any sample well or vessel of racks R_1 - R_n at any given time during operation of sampling system **10**.

High-pressure pump P_2 can be any pump suitable for moving fluid at pressures normally used for injecting samples into analytical instruments.

Preferably, high-pressure pump P_2 can operate at different flow rates and/or pressures. For example, high-pressure pump P_2 can be the type of pump conventionally used to inject samples into an HPLC instrument. One example of a suitable commercially available pump is a Gilson™ Model 307 isocratic pump available from Gilson, Inc., Middleton, Wisconsin. High-pressure pump P_2 communicates with solvent reservoir **51** through a liquid transfer line L_8, or alternatively could communicate with a separate solvent reservoir (not shown).

Analytical instrument **AI** can be any instrument used in the art to analyze samples. In a specific application of the invention, analytical instrument **AI** constitutes a mass spectrometer, although the invention is not limited to such an instrument. Examples of other types of instruments suitable for use in connection with the invention include those designed to carry out optical spectrochemical analysis in the UV, visible, and IR spectra (e.g., spectroscopy and spectrophotometry). Moreover, the particular analytical instrument **AI** used in the present invention is not limited by any sample size restrictions. The advantages provided by the invention can be realized using an analytical instrument **AI** capable of either macro analysis (0.1 g or greater sample weight), semimicro or meso analysis (0.01 to 0.1 g), micro analysis (10^{-4} to 10^{-2} g), ultramicro analysis (10^{-4} g or less), or ultra-trace analysis. Analytical instrument **AI** could be capable of performing qualitative and/or quantitative analyses. Analytical instrument **AI** could be capable of performing multiple-species analyses in either a sequential, simultaneous, or parallel manner. In addition, analyzing instrument **AI** could comprise more than one analytical modality (e.g., two mass spectrometers, a mass spectrometer and a fraction collector, and so on).

Figures 3A – 3C illustrate three modes attainable by valve assembly **VA** when valve assembly **VA** is provided in the two-valve configuration. Specifically, Figure 3A illustrates a sample injection/needle rinse mode, Figure 3B illustrates a sample loop load/instrument flush mode, and Figure 3C illustrates a sample loop flush/instrument flush mode. These modes are attained by selectively adjusting the respective rotary valve bodies of first and second valves V_1 and V_2. The adjustments have the effect of selecting which

pairs of ports on each valve V_1 and V_2 become fluidly interconnected by the internal passages that rotate with their respective valve bodies, as well as which components of sampling system **10** are actively associated with the flow paths defined by the three modes. As appreciated by persons skilled in the art, the valve bodies are actuated by stepper motors or equivalent mechanisms capable of precisely indexing the valve bodies. In the present invention, the actuating movements required to effect the valve adjustments are initiated and controlled by drive signals supplied from electronic control unit **100** (see Figure 9).

In the exemplary configurations illustrated in Figures 3A – 3C, valve V_1 includes ports **A - F** and adjustable internal passages **a - c**, and valve V_2 includes ports **G - L** and adjustable internal passages **d - f**. The ends of sample loop **SL** are fluidly connected at ports **A** and **D**, respectively, of valve V_1. Liquid transfer line L_7 fluidly interconnects valves V_1 and V_2 at port **C** of valve V_1 and port **K** of valve V_2. Liquid transfer line L_2 fluidly interconnects syringe pump P_1 of liquid handling apparatus **20** with valve V_1 at port **B**. Liquid transfer line L_3 fluidly interconnects high-pressure pump P_2 with valve V_1 at port **F**. Liquid transfer line L_4 fluidly interconnects analytical instrument **AI** with valve V_1 at port **E**. Liquid transfer line L_6 fluidly interconnects sampling needle **SN** (or a suitable, alternative sample source) with valve V_2 at port **L**. Finally, liquid transfer line L_5 fluidly interconnects waste receptacle **W** with valve V_2 at port **J**.

Referring specifically to Figure 3A, valves V_1 and V_2 are positioned at the sample injection/needle rinse mode. This mode enables a sample contained in sample loop **SL** to be injected into analytical instrument **AI** and, simultaneously, sampling needle **SN** to be rinsed with a suitable solvent. Valve V_1 is positioned such that internal passage **a** fluidly interconnects port **B** and port **C**, internal passage **b** fluidly interconnects port **D** and port **E**, and internal passage **c** fluidly interconnects port **F** and port **A**. Valve V_2 is positioned such that internal passage **f** fluidly interconnects port **L** and port **K**. In the sample injection/needle rinse mode, valves V_1 and V_2 are positioned to define two flow paths: a sample injection flow path $P_2 \rightarrow L_3 \rightarrow$ **F** $\rightarrow$ **c** $\rightarrow$ **A** $\rightarrow$ **SL** $\rightarrow$ **D** $\rightarrow$ **b** $\rightarrow$ **E**

→ L_4 → **AI**; and a sampling needle rinsing flow path P_1 → L_2 → **B** → **a** → **C** → L_7 → **K** → **f** → **L** → L_6 → **SN**.

In the sample injection flow path, a sample previously loaded into sample loop **SL** is injected into analytical instrument **AI** by moving through port **D**, internal passage **b**, port **E**, and liquid transfer line L_4. The sample moves and is thus injected into analytical instrument **AI** under the influence of high-pressure pump P_2, which creates fluid pressure in transfer line L_3, port **F**, internal passage **c**, and port **A**. In the sampling needle rinsing flow path, syringe pump P_1 draws solvent from solvent reservoir **51** (see Figure 1) through liquid transfer line L_1, and pushes the solvent through liquid transfer line L_2, port **B**, internal passage **a**, port **C**, liquid transfer line L_7, port **K**, internal passage **f**, port **L**, liquid transfer line L_6, and sampling needle **SN**. During this mode, it is preferable that a control signal be sent to robot apparatus **30** (see Figure 1) to position sampling needle **SN** at an appropriate waste receptacle, such as waste receptacle **W**, or a rinsing station for collection of the used solvent.

Referring specifically to Figure 3B, valves V_1 and V_2 are positioned at the sample loop load/instrument flush mode. This mode enables a sample of precise volume to be loaded into sample loop **SL** and, simultaneously, analytical instrument **AI** to be flushed with a clean solvent. Valve V_1 has been rotated, and is now positioned such that internal passage **a** fluidly interconnects port **C** and port **D**, internal passage **b** fluidly interconnects port **E** and port **F**, and internal passage **c** fluidly interconnects port **C** and port **B**. The position of valve V_2 is maintained at the position shown in Figure 3A, such that internal passage **f** fluidly interconnects port **K** and port **L**. In the sample loop load/instrument flush mode, valves V_1 and V_2 are positioned to define two flow paths: a sample loading flow path **SN** → L_6 → **L** → **f** → **K** → L_7 → **C** → **a** → **D** → **SL** → **A** → **c** → **B** → L_2 → P_1; and an instrument flushing flow path P_2 → L_3 → **F** → **b** → **E** → L_4 → **AI**.

In the sample loading flow path, a sample that has been drawn into sampling needle **SN** moves through transfer line L_6, port **L**, internal passage **f**, port **K**, transfer line L_7, port **C**, internal passage **a**, port **D**, and into sample loop **SL**. The sample is pulled by the vacuum induced by syringe pump P_1 through

transfer line L_2, port **B**, internal passage **c**, and port **A**. The particular sample loaded in sample loop **SL** is selected by sending appropriate control signals to liquid handling apparatus **20** (see Figure 1). As an example of the loading sequence, robotic assembly **30** is caused to move sampling needle **SN** into position over a selected vessel of the array of vessels contained on a selected one of racks $R_1 - R_n$, after which time sampling needle **SN** is lowered into the selected vessel and syringe pump P_1 activated to cause the selected sample (or an aliquot thereof) to be aspirated into sampling needle **SN**. In the instrument flushing flow path, solvent is circulated by high-pressure pump P_2 into analytical instrument **AI** through transfer line L_3, port **F**, internal passage **b**, port **E**, and transfer line L_4. Analytical instrument **AI** is considered to be completely flushed when the only artifacts observed by analytical instrument **AI** are those characterizing the solvent used. As appreciated by persons skilled in the art, analytical instrument **AI** is typically equipped with means for collecting all substances it receives. For example, in the case of a mass spectrometer that ionizes incoming substances, an air handling system takes away the vapors produced by or sent through the mass spectrometer.

Referring specifically to Figure 3C, valves V_1 and V_2 are positioned at the sample loop flush/instrument flush mode. This mode enables sample loop **SL** to be flushed with a suitable solvent and, simultaneously, analytical instrument **AI** to be flushed with a suitable solvent. The position of valve V_1 is maintained at the position shown in Figure 3B, such that internal passage **a** fluidly interconnects port **C** and port **D**, internal passage **b** fluidly interconnects port **E** and port **F**, and internal passage **c** fluidly interconnects port **A** and port **B**. Valve V_2 has been rotated, and is now positioned such that internal passage **d** fluidly interconnects port **J** and port **K**. In the sample loop flush/instrument flush mode, valves V_1 and V_2 are positioned to define two flow paths: a sample loop flushing flow path $P_1 \rightarrow L_2 \rightarrow$ **B** $\rightarrow$ **c** $\rightarrow$ **A** $\rightarrow$ **SL** $\rightarrow$ **D** $\rightarrow$ **a** $\rightarrow$ **C** $\rightarrow L_7 \rightarrow$ **K** $\rightarrow$ **d** $\rightarrow$ **J** $\rightarrow L_5 \rightarrow$ **W**; and the instrument flushing flow path $P_2 \rightarrow L_3 \rightarrow$ **F** $\rightarrow$ **b** $\rightarrow$ **E** $\rightarrow L_4 \rightarrow$ **AI** described hereinabove with reference to Figure 3B.

In the sample loop flushing flow path, syringe pump P_1 is activated to draw solvent from solvent reservoir **51** through liquid transfer line L_1 (see Figure

1) and to push the solvent through transfer line L_2, port **B**, internal passage **c**, and port **A**, thereby causing a sample residing in sample loop **SL** to be pushed through port **D**, internal passage **a**, port **C**, transfer line L_7, port **K**, internal passage **d**, port **J**, transfer line L_5, and into waste receptacle **W**. As described hereinabove, the instrument flushing flow path can continue to be used to flush analytical instrument **AI**.

It can thus be seen that valve assembly **VA** is capable of loading sample loop **SL** while flushing analytical instrument **AI**, injecting the sample from sample loop **SL** while rinsing sampling needle **SN**, and flushing the remaining sample in sample loop **SL** to waste while flushing clean solvent into analytical instrument **AI**. Moreover, at each state attained by valve assembly **VA**, some form of fluid, whether containing a sample or a rinsing medium, is being circulated through analytical instrument **AI**. The operation of valve assembly **VA** and the rapid switching of valve assembly **VA** among its three modes or states significantly increases the throughput of sampling data acquisition processes as compared to, for example, conventional injection port-based systems due to the decreased inter-sample delay time needed to reach acceptable carryover requirements and the time savings realized by eliminating the injection port.

Referring now to Figure 4, a valve assembly, generally designated **VA'**, is illustrated according to an alternative, single-valve embodiment of the invention. Valve assembly **VA'** is a linear valve design in which a valve body **81** slides within a stationary housing structure **83**. Valve body **81** is actuated by a suitable actuator (not shown, but could be, e.g., a solenoid, pneumatic cylinder, hydraulic cylinder, motor, worm drive, or the like) through a suitable arm or other linkage mechanism **85**. Valve body **81** can be actuated by a reciprocating, double-acting actuator of known design, or alternatively could be actuated in alternative directions respectively by two oppositely disposed actuators (in which case an additional, oppositely disposed linkage mechanism **85** would be required). Housing structure **83** has an upper portion **83A** and a lower portion **83B**. Valve assembly **VA'** has eight ports **A – H**. Upper portion **83A** of housing structure **83** includes ports **A**, **B** and **C**, and lower portion **83B**

includes ports **D**, **E** and **F**. Valve body **81** includes ports **G** and **H**, which preferably are internally disposed with respect to housing structure **83**. Valve body **81** also includes six internal passages **a – f**. The centermost passages, internal passages **c** and **d**, are disposed in opposing, linear alignment with each other and terminate at ports **G** and **H**, respectively. Sample loop **SL** is fluidly connected to ports **G** and **H**. Sample loop **SL** moves with valve body **81** and preferably is disposed internally with respect to housing structure **83** but could be located externally, connecting to ports **G** and **H**.

In the position of valve body **81** shown in Figure 4, internal passage **b** fluidly interconnects ports **A** and **D**, internal passage **c** fluidly interconnects ports **B** and **G**, internal passage **d** fluidly interconnects ports **H** and **E**, and internal passage **e** fluidly interconnects ports **C** and **F**. Additionally, internal passages **a** and **f** are effectively plugged at their respective openings by upper and lower portions **83A** and **83B** of housing structure **83**. It can be seen, however, that as valve body **81** is selectively and controllably actuated to the left and to the right, different internal passages **a – f** are brought into fluid communication with different ports **A – F** in order to alter the fluid circuit with which valve assembly **VA'** is associated. As indicated in Figure 4, internal passage **c** is always fluidly associated with port **G** and internal passage **d** is likewise always fluidly associated with port **H**.

Figures 5A – 5C illustrate the three modes attainable by valve assembly **VA'** when valve assembly **VA'** is provided in the linear valve configuration illustrated in Figure 4. Specifically, Figure 5A illustrates the sample injection/needle rinse mode, Figure 5B illustrates the sample loop load/instrument flush mode, and Figure 5C illustrates the sample loop flush/instrument flush mode. These modes are attained by selectively adjusting valve body **81** with respect to housing structure **83** (see Figure 4). The adjustments have the effect of selecting which ports **A -- H** become fluidly interconnected by internal passages **a -- f**, as well as which components of sampling system **10** are actively associated with the flow paths defined by the three modes. In the present invention, the actuating movements required to effect the valve adjustments are initiated and controlled by drive signals

supplied from electronic control unit **100** (see Figure 9) to the actuator connected to linkage mechanism **85** (see Figure 4).

In the exemplary configurations illustrated in Figures 5A – 5C, fluid connections are made at ports **A - H** of valve assembly **VA'** from various components of sampling system **10** as in the case of valve assembly **VA** illustrated in Figures 3A – 3C. High-pressure pump P_2 of liquid handling apparatus **20** is connected to both ports **A** and **B** by dividing the flow through liquid transfer line L_3 into two separate flow paths respectively directed to ports **A** and **B**, using a flow splitter or tee connection and two additional liquid transfer lines (not shown). Alternatively, two separate high-pressure pumps P_2 (or a high-pressure pump and a syringe pump) and corresponding liquid transfer lines L_3 could be provided for transporting solvent through ports **A** and **B**, respectively. Liquid transfer line L_2 fluidly interconnects syringe pump P_1 with valve assembly **VA'** at port **C**. Liquid transfer line L_5 fluidly interconnects waste receptacle **W** with valve assembly **VA'** at port **D**. Liquid transfer line L_4 fluidly interconnects analytical instrument **AI** with valve assembly **VA'** at port **E**. Liquid transfer line L_6 fluidly interconnects sampling needle **SN** or other sample source with valve assembly **VA'** at port **F**. Sample loop **SL** fluidly communicates with valve assembly **VA'** at ports **G** and **H**.

Referring specifically to Figure 5A, valve body **81** is positioned at the sample injection/needle rinse mode. Valve body **81** is positioned such that internal passage **a** is plugged, internal passage **b** fluidly interconnects ports **A** and **D**, internal passage **c** fluidly interconnects ports **B** and **G**, internal passage **d** fluidly interconnects ports **H** and **E**, internal passage **e** fluidly interconnects ports **C** and **F**, and internal passage **f** is plugged. In the sample injection/needle rinse mode, valve body **81** is positioned to define two flow paths: a sample injection flow path P_2 → L_3 → **B** → **c** → **G** → **SL** → **H** → **d** → **E** → L_4 → **AI**; and a sampling needle rinsing flow path P_1 → L_2 → **C** → **e** → **F** → L_6 → **SN**. In the sample injection flow path, a sample previously loaded into sample loop **SL** is injected into analytical instrument **AI** by moving through port **H**, internal passage **d**, port **E**, and liquid transfer line L_4. The sample moves and is thus injected into analytical instrument **AI** under the influence of high-

pressure pump P_2, which creates fluid pressure in transfer line L_3, port **B**, internal passage **c**, and port **G**. In the sampling needle rinsing flow path, syringe pump P_1 draws solvent from solvent reservoir **51** through liquid transfer line L_1 (see Figure 1), and pushes the solvent through liquid transfer line L_2, port **C**, internal passage **e**, port **F**, liquid transfer line L_6, and sampling needle **SN**. During this mode, it is preferable that a control signal be sent to robot apparatus **30** (see Figure 1) to position sampling needle **SN** at an appropriate waste receptacle, such as waste receptacle **W**, or a rinsing station for collection of the used solvent.

Referring specifically to Figure 5B, valve body **81** is positioned at the sample loop load/instrument flush mode. Valve body **81** is positioned such that internal passage **a** fluidly interconnects ports **A** and **D**, internal passage **b** fluidly interconnects ports **B** and **E**, internal passage **c** fluidly interconnects ports **C** and **G**, internal passage **d** fluidly interconnects ports **H** and **F**, and internal passages **e** and **f** are plugged. In the sample loop load/instrument flush mode, valve body **81** is positioned to define two flow paths: a sample loading flow path **SN** → L_6 → **F** → **d** → **H** → **SL** → **G** → **c** → **C** → L_2 → P_1; and an instrument flushing flow path P_2 → L_3 → **B** → **b** → **E** → L_4 → **AI**. In the sample loading flow path, a sample that has been drawn into sampling needle **SN** moves through transfer line L_6, port **F**, internal passage **d**, port **H**, and into sample loop **SL**. The sample is pulled by the vacuum induced by syringe pump P_1 through transfer line L_2, port **C**, internal passage **c**, and port **G**. The particular sample loaded in sample loop **SL** is selected by sending appropriate control signals to liquid handling apparatus **20** and robotic assembly **30** (see Figure 1) as described hereinabove. In the instrument flushing flow path, solvent is circulated by high-pressure pump P_2 into analytical instrument **AI** through transfer line L_3, port **B**, internal passage **b**, port **E**, and transfer line L_4.

Referring specifically to Figure 5C, valve body **81** is positioned at the sample loop flush/instrument flush mode. Valve body **81** is positioned such that internal passages **a** and **b** are plugged, internal passage **c** fluidly interconnects ports **A** and **G**, internal passage **d** fluidly interconnects ports **H** and **D**, internal passage **e** fluidly interconnects ports **B** and **E**, and internal

passage **f** fluidly interconnects ports **C** and **F**. In the sample loop flush/instrument flush mode, valve body **81** is positioned to define two flow paths: a sample loop flushing flow path P_2 → L_3 → **A** → **c** → **G** → **SL** → **H** → **d** → **D** → L_5 → **W**; and another instrument flushing flow path P_2 → L_3 → **B** → **e** → **E** → L_4 → **AI**. In the sample loop flushing flow path, high-pressure pump P_2 is activated to draw solvent from solvent reservoir **51** through liquid transfer line L_8 (see Figure 1) and to push the solvent through transfer line L_3, port **A**, internal passage **c**, and port **G**, thereby causing a sample residing in sample loop **SL** to be pushed through port **H**, internal passage **d**, port **D**, transfer line L_5, and into waste receptacle **W**. As described hereinabove, the instrument flushing flow path can be used to flush analytical instrument **AI**.

Referring now to Figures 6 and 7A – 7C, a valve assembly, generally designated **VA"**, is illustrated according to another alternative, single-valve embodiment of the invention. Valve assembly **VA"** is a rotary design in which a valve body **91** rotates in relation to a stationary upper valve structure **93A** and a stationary lower valve structure **93B**. Valve body **91** is preferably cylindrical, and upper and lower valve structures **93A** and **93B** are preferably disk-shaped. Valve body **91** is actuated by a suitable actuator (not shown, but could be, e.g., a solenoid, pneumatic cylinder, hydraulic cylinder, motor, or the like) through a suitable arm or other linkage mechanism (not shown). The linkage mechanism could be, for example, an endless member such as a belt that operatively engages the outer lateral surface of valve body **91**, or could be a rotatable shaft that is connected to valve body **91** through a bore (not shown) in upper valve structure **93A** or lower valve structure **93B**. Valve assembly **VA"** has eight ports **A** – **H**. Upper valve structure **93A** includes ports **A**, **B** and **C**, and lower valve structure **93B** includes ports **D**, **E** and **F**. Valve body **91** includes ports **G** and **H**, which preferably are internally disposed with respect to a structure (not shown) that houses valve body **91**. Valve body **91** also includes four internal passages **a** – **d**. Internal passages **b** and **c** are disposed in opposing, linear alignment with each other and terminate at ports **G** and **H**, respectively. Sample loop **SL** is fluidly connected to ports **G** and **H** and rotates with valve body **91**. As valve body **91** is selectively and controllably actuated to

rotate with respect to upper and lower valve structures **93A** and **93B**, different internal passages **a – d** are brought into fluid communication with different ports **A – F** in order to alter the fluid circuit with which valve assembly **VA"** is associated. As indicated in Figures 6 and 7C, internal passage **b** is always fluidly associated with port **G** and internal passage **c** is likewise always fluidly associated with port **H**.

Figures 8A – 8C illustrate the three modes attainable by valve assembly **VA"** when valve assembly **VA"** is provided in the rotary valve configuration illustrated in Figures 6 and 7A -- 7C. Specifically, Figure 8A illustrates the sample injection/needle rinse mode, Figure 8B illustrates the sample loop load/instrument flush mode, and Figure 8C illustrates the sample loop flush/instrument flush mode. These modes are attained by selectively adjusting valve body **91** with respect to upper and lower valve structures **93A** and **93B** (see Figures 6 and 7A – 7C). The adjustments have the effect of selecting which ports **A -- H** become fluidly interconnected by internal passages **a -- d**, as well as which components of sampling system **10** are actively associated with the flow paths defined by the three modes. In the present invention, the actuating movements required to effect the valve adjustments are initiated and controlled by drive signals supplied from electronic control unit **100** (see Figure 9) to the actuator associated with valve assembly **VA"**.

In the exemplary configurations illustrated in Figures 8A – 8C, the fluid connections made at ports **A - H** of valve assembly **VA"** are roughly analogous to those illustrated in Figures 5A – 5C regarding valve assembly **VA'**. High-pressure pump P_2 of liquid handling apparatus **20** is connected to both ports **A** and **B** by dividing the flow through liquid transfer line L_3 into two separate flow paths respectively directed to ports **A** and **B**, using a flow splitter or tee connection and two additional liquid transfer lines (not shown). Alternatively, two separate high-pressure pumps P_2 (or syringe pumps) and corresponding liquid transfer lines L_3 could be provided for transporting solvent through ports **A** and **B**. Liquid transfer line L_2 fluidly interconnects syringe pump P_1 with valve assembly **VA"** at port **C**. Liquid transfer line L_5 fluidly interconnects waste receptacle **W** with valve assembly **VA"** at port **D**. Liquid transfer line L_4 fluidly

interconnects analytical instrument **AI** with valve assembly **VA"** at port **E**. Liquid transfer line L_6 fluidly interconnects sampling needle **SN** with valve assembly **VA"** at port **F**. Sample loop **SL** fluidly communicates with valve assembly **VA"** at ports **G** and **H**.

Referring specifically to Figure 8A, valve body **91** is positioned at the sample injection/needle rinse mode. Valve body **91** is positioned such that internal passage **a** fluidly interconnects ports **A** and **D**, internal passage **b** fluidly interconnects ports **B** and **G**, internal passage **c** fluidly interconnects ports **H** and **E**, and internal passage **d** fluidly interconnects ports **C** and **F**. In the sample injection/needle rinse mode, valve body **91** is positioned to define two flow paths: a sample injection flow path $P_2 \rightarrow L_3 \rightarrow$ **B** $\rightarrow$ **b** $\rightarrow$ **G** $\rightarrow$ **SL** $\rightarrow$ **H** $\rightarrow$ **c** $\rightarrow$ **E** $\rightarrow L_4 \rightarrow$ **AI**; and a sampling needle rinsing flow path $P_1 \rightarrow L_2 \rightarrow$ **C** $\rightarrow$ **d** $\rightarrow$ **F** $\rightarrow L_6 \rightarrow$ **SN**. In the sample injection flow path, a sample previously loaded into sample loop **SL** is injected into analytical instrument **AI** by moving through port **H**, internal passage **c**, port **E**, and liquid transfer line L_4. The sample moves and is thus injected into analytical instrument **AI** under the influence of high-pressure pump P_2, which creates fluid pressure in transfer line L_3, port **B**, internal passage **b**, and port **G**. In the sampling needle rinsing flow path, syringe pump P_1 draws solvent from solvent reservoir **51** through liquid transfer line L_1 (see Figure 1), and pushes the solvent through liquid transfer line L_2, port **C**, internal passage **d**, port **F**, liquid transfer line L_6, and sampling needle **SN**. During this mode, it is preferable that a control signal be sent to robot apparatus **30** (see Figure 1) to position sampling needle **SN** at an appropriate waste receptacle, such as waste receptacle **W**, or a rinsing station for collection of the used solvent.

Referring specifically to Figure 8B, valve body **91** is positioned at the sample loop load/instrument flush mode. Valve body **91** has been rotated, and is now positioned such that internal passage **a** fluidly interconnects ports **B** and **E**, internal passage **b** fluidly interconnects ports **C** and **G**, internal passage **c** fluidly interconnects ports **H** and port **F**, and internal passage **d** fluidly interconnects ports **A** and **D**. In the sample loop load/instrument flush mode, valve body **91** is positioned to define two flow paths: a sample loading flow

path **SN** → L_6 → **F** → **c** → **H** → **SL** → **G** → **b** → **C** → L_2 → P_1; and an instrument flushing flow path P_2 → L_3 → **B** → **a** → **E** → L_4 → **AI**. In the sample loading flow path, a sample that has been drawn into sampling needle **SN** moves through transfer line L_6, port **F**, internal passage **c**, port **H**, and into sample loop **SL**. The sample is pulled by the vacuum induced by syringe pump P_1 through transfer line L_2, port **C**, internal passage **b**, and port **G**. The particular sample loaded in sample loop **SL** is selected by sending appropriate control signals to liquid handling apparatus **20** and robotic assembly **30** (see Figure 1) as described hereinabove. In the instrument flushing flow path, solvent is circulated by high-pressure pump P_2 into analytical instrument **AI** through transfer line L_3, port **B**, internal passage **a**, port **E**, and transfer line L_4.

Referring specifically to Figure 8C, valve body **91** is positioned at the sample loop flush/instrument flush mode. Valve body **91** has again been rotated, and is now positioned such that internal passage **a** fluidly interconnects ports **C** and **F**, internal passage **b** fluidly interconnects ports **A** and **G**, internal passage **c** fluidly interconnects ports **H** and **D**, and internal passage **d** fluidly interconnects ports **B** and **E**. In the sample loop flush/instrument flush mode, valve body **91** is positioned to define two flow paths: a sample loop flushing flow path P_2 → L_3 → **A** → **b** → **G** → **SL** → **H** → **c** → **D** → L_5 → **W**; and another instrument flushing flow path P_2 → L_3 → **B** → **d** → **E** → L_4 → **AI**. In the sample loop flushing flow path, high-pressure pump P_2 is activated to draw solvent from solvent reservoir **51** through liquid transfer line L_8 (see Figure 1) and to push the solvent through transfer line L_2, port **A**, internal passage **b**, and port **G**, thereby causing a sample residing in sample loop **SL** to be pushed through port **H**, internal passage **c**, port **D**, transfer line L_5, and into waste receptacle **W**. As described hereinabove, the instrument flushing flow path can be used to flush analytical instrument **AI**.

It will be understood that sampling system **10** illustrated in Figure 1 can be modified or reconfigured to accommodate valve assembly **VA'** or valve assembly **VA"**. For the remainder of the present disclosure, references to valve assembly VA will be understood to also encompass valve assemblies **VA'** and **VA"**.

Figure 9 is a schematic diagram illustrating an exemplary operational control environment for the invention. The environment generally comprises an electronic control unit such as a computer **100** that can send output signals to and receive input signals from liquid handling apparatus **20** (including the operational components of robotic assembly **30**, syringe pump P_1, and high-pressure pump P_2), valve assembly **VA**, and analytical instrument **AI** over suitable electronic transmission lines **102**, **104** and **106**, respectively (or, alternatively, by wireless means). Computer **100** can be provided as a commercially available personal computer with a standard operating system such as WINDOWS®, UNIX®, LINUX®, or the like. In addition, computer **100** preferably communicates over an electronic transmission line **108** with a peripheral user interface **110** to enable the user to input commands (e.g., by way of a keyboard) and to view output (e.g., by way of a monitor). Computer **100** processes data and instructions provided by control software **112**. Control software **112** can comprise a single set of instructions, or could comprise a plurality of suitably interfaced and compatible modules or programs. For example, control software **112** could comprise several discrete objects each consisting of function-specific routines and data structures. Non-limiting examples of such objects include robotic drive, valve actuation, pump actuation, and analytic instrument control objects.

Figures 10A and 10B illustrate an example of a sampling and data acquisition process performed by sampling system **10** under the control of control software **112**. Referring to Figure 10A, block **201** designates the start of the sampling and data acquisition process. At block **203**, high-pressure pump P_2 is set to a baseline flow rate. At block **205**, signals are sent by control software **112** to liquid handling apparatus **20** and valve assembly **VA** to initiate the sample loop flush/instrument flush mode. At block **207**, high-pressure pump P_2 is set to a high flow rate suitable for flushing the liquid lines, ports and passages that are fluidly associated with analytical instrument **AI** and valve assembly **VA**. At this point, valve assembly **VA** has been set to the position illustrated in Figure 3C at which the instrument flushing flow path is defined, and solvent flows to analytical instrument **AI**. At block **209**, solvent continues to

flow to analytical instrument **AI** for a predetermined time so as to minimize carryover. At block **211**, high-pressure pump P_2 is reset to the baseline flow rate. At block **213**, solvent continues to flow through the instrument flushing flow path while control software **112** waits for analytical instrument **AI** to be readied for the ensuing data acquisition of a sample.

The successive events represented by blocks **215 - 225** occur simultaneously with the successive events represented by blocks **205 - 213**. At block **215**, valve assembly **VA** has been set to the position illustrated in Figure 3C at which the sample loop flushing flow path is defined (which is the same position at which the instrument flushing flow path is defined). At block **217**, syringe pump P_1 is activated to aspirate solvent from solvent reservoir **51** into the sample loop flushing flow path. At block **219**, solvent flowing through the sample loop flushing flow path is dispensed through sample loop **SL** and into waste receptacle **W** under the influence of syringe pump P_1. At block **221**, valve assembly **VA** is set to the sample injection/needle rinse mode illustrated in Figure 3A. At block **223**, syringe pump P_1 is activated to aspirate solvent from solvent reservoir **51** into the sampling needle rinsing flow path. At block **225**, solvent flowing through the sampling needle rinsing flow path is dispensed through sample needle **SN** under the influence of syringe pump P_1. At block **227**, control software **112** waits for the operations represented by blocks **205 – 213** and **215 -- 225** to complete before proceeding to the following sample loading and sample injection procedures.

Referring now to Figure 10B, at block **229**, signals are sent by control software **112** to liquid handling apparatus **30**, valve assembly **VA**, and analyzing instrument **AI** to initiate the sample loop load/instrument flush mode and the sample injection/needle rinse mode. At block **231**, control software **112** sends a signal to robotic assembly **30** to transport sampling needle **SN** to predetermined coordinates that define a selected rack R_1 - R_n and a specific sample vessel selected from the array of sample vessels located on the rack R_1 - R_n . Once robotic assembly **30** has reached the desired coordinates, robotic assembly **30** causes the tip of sampling needle **SN** to enter the selected sample vessel. At block **233**, valve assembly **VA** is set to the position

illustrated in Figure 3B at which the sample loop loading flow path is defined. At block **235**, syringe pump P_1 is activated to aspirate the particular sample contained in the selected sample vessel into sampling needle **SN** and the sample is transferred through the sample loop loading flow path into sample loop **SL**. At block **237**, once the sample is loaded in sample loop **SL**, valve assembly **VA** is set to the position illustrated in Figure 3A at which the sample injection path is defined. Control software **112** sends a signal to high-pressure pump P_2 to begin injection of the sample contained in sample loop **SL** into analytical instrument **AI**. At block **239**, control software **112** initiates a count based on flow rate to determine a time at which sample loop **SL** has been partially emptied. After this wait time has elapsed, at block **241**, control software **112** waits while the respective operations of liquid handling apparatus **20**, valve assembly **VA**, and analyzing instrument **AI** represented by blocks **231 – 239** complete in preparation for data acquisition by analytical instrument **AI**.

At block **243**, control software **112** sends a signal to analytical instrument **AI** to initiate data acquisition from the sample. At block **245**, control software **112** sets the flow rate of high-pressure pump P_2 to an intermediate level to accelerate the sample into analytical instrument **AI**. At block **247**, control software **112** waits for the sample to arrive at analytical instrument **AI** and then, at block **249**, backs the flow rate of high-pressure pump P_2 down to the baseline level while the sample is flowing into analytical instrument **AI**. As indicated in Figures 10A and 10B, this entire sampling and data acquisition cycle is repeated for the next sample.

Referring now to Figure 11, in one aspect of the method of the invention, a data-driven decisional process is provided to enhance sample throughput by enabling the sample delivery process to act on feedback received from the data acquisition/analysis process. In this data-driven decisional process, control software **112** makes decisions, such as whether to reject a particular sample during acquisition thereof, or divert a particular sample to a different sample path or analytical instrument, or permit analytical instrument **AI** to complete the acquisition of that sample, based on feedback from the data acquisition/analysis process. By this method, each sample is processed

without the time penalties associated with conventional systems, which require the entire sample to be pumped through the system at a nominal flow rate regardless of whether or not data is to be acquired.

Block **261** designates the start of the sampling and data acquisition process, and hence is equivalent to block **201** in Figure 10A. Block **263** designates the sample loop flush/instrument flush mode illustrated in Figure 3C and described hereinabove. Block **265** designates the sample loop load/instrument flush mode illustrated in Figure 3B and described hereinabove. Blocks **267** and **269** designate the sample injection/needle rinse mode illustrated in Figure 3A and described hereinabove. At block **271**, the sample (or at least an initial portion of the sample that has been introduced into analytical instrument **AI**) is analyzed by control software **112** in real time as it is acquired by analytical instrument **AI**. At block **273**, control software **112** decides whether the sample, the system, and/or instrumentation thereof meets predetermined decision criteria. These criteria can include values based on certain properties of the sample and/or diagnostics or operational/functional states of the system or instrumentation. Non-limiting examples of decision criteria include insufficient sample intensity, thresholding criteria, noise criteria, criteria associated with the presence or absence of a particular peak in a spectrum, and/or criteria associated with the status of analyzing instrument **AI**. In general, decisions are made by comparing measured, detected, or instrumentation/system-generated values against the predetermined or stored criteria, and determining whether a pass or fail condition exists. For purposes of the present disclosure, all such values used for comparison with the decisional criteria, whether or not such values are derived from the system, its instrumentation, or the sample itself, are characterized as being properties of the sample that are obtained by taking some type of measurement of the sample.

If control software **112** determines that the sample fails to meet the decision criteria, the current method of data acquisition for that sample is terminated. In one alternative, the remaining sample residing in sample loop **SL** is discarded at block **275**, and the process then returns to block **263**, where

the sample loop **SL**, analytical instrument **AI**, and all associated fluid conduits are flushed in preparation for data acquisition of the next sample. In another alternative, at block **277**, control software **112** can be programmed to cause either a change in the sample injection path or a change in the analytical method to be implemented. An example of changing the sample injection path is to divert the remaining sample (i.e., that portion of the sample that has not yet been processed by or introduced into analytical instrument **AI**) away from analytical instrument **AI** to another type of instrument or device for further processing. For instance, in the case where analytical instrument **AI** is a mass spectrometer, the other instrument or device could be a UV spectrophotometer, a fraction collector, a liquid chromatography device, or another mass spectrometer. An example of selecting or altering a different analytical method is changing one or more settings of analytical instrument **AI**. For instance, in the case where analytical instrument **AI** is a mass spectrometer, control software **112** could cause the mass spectrometer to scan for a different range of mass/charge ratios. After the sample is further processed, it is discarded at block **279**, and the process then returns to block **263**, where the sample loop **SL**, analytical instrument **AI**, and all associated fluid conduits are flushed in preparation for data acquisition of the next sample.

On the other hand, if control software **112** determines that the sample meets the decision criteria, at block **281**, additional data for that sample can be acquired using the same or new analytical parameters. Data acquisition for that sample is permitted to continue to completion, as indicated by block **283**. As shown in Figure 11, the remaining sample is then discarded at block **285**, and the process returns to block **263**, where the sample loop **SL**, analytical instrument **AI**, and all associated fluid conduits are flushed in preparation for data acquisition of the next sample.

Figure 12 illustrates a plot of intensity in counts per second (cps) versus time for a data acquisition process carried out in accordance with the present invention. For this process run, sampling system **10** illustrated in Figure 1 was equipped with a dual-valve valve assembly **VA** as described hereinabove with reference to Figures 3A – 3C and an analytical instrument **AI** in the form of a

mass spectrometer. The intensity data was obtained for the 570 – 576 atomic mass unit (amu) range for eight consecutive samples. The samples were processed by the mass spectrometer in 55-second cycle times, with 14 seconds of data acquisition time at maximum intensity for each cycle. No data were acquired during the inter-sample times so that intensity could be plotted as a baseline. The results shown in Figure 12 demonstrate the capabilities of the invention to achieve rapid-fire sample introduction without carryover.

Figure 13 illustrates a plot of intensity versus time for a data acquisition process carried out in accordance with the present invention, in comparison to a process carried out by a conventional system. The data acquisition times using the conventional system were approximately 2:39 minutes, while the data acquisition times achieved by the present invention were approximately 1:59 minutes. Figure 13 thus evidences an approximately 25% improvement in sample throughput by the invention over the conventional system.

It will be understood that various details of the invention may be changed without departing from the scope of the invention. Furthermore, the foregoing description is for the purpose of illustration only, and not for the purpose of limitation—the invention being defined by the claims.

CLAIMS

What is claimed is:

1. A method for acquiring data from a sample, comprising the steps of:
   (a) transferring at least an initial portion of a sample into an analytical instrument;
   (b) causing the analytical instrument to acquire data from the initial portion of the sample;
   (c) while the analytical instrument is acquiring data, measuring one or more properties of the initial portion of the sample;
   (d) determining whether the initial portion of the sample meets one or more decision criteria based on the one or more properties measured; and
   (e) in response to determining the initial portion of the sample to have failed to meet any of the one or more decision criteria, causing the analytical instrument to cease acquiring data from the initial portion of the sample, or in response to determining the initial portion of the sample to have met all of the one or more decision criteria transferring an additional portion of the sample into the analytical instrument and causing the analytical instrument to acquire data from the additional portion.
2. The method according to claim 1 wherein the initial portion of the sample is transferred into the analytical instrument from a sample reservoir.
3. The method according to claim 2 comprising the step of, prior to transferring the initial portion of the sample into the analytical instrument, loading the sample into the sample reservoir from a sample conduit.
4. The method according to claim 3 comprising the step of flushing the analytical instrument while the sample reservoir is being loaded.
5. The method according to claim 3 comprising the step of flushing the sample conduit while the initial portion of the sample is being transferred into the analytical instrument.

6. The method according to claim 5 wherein the sample conduit comprises a sampling probe.

7. The method according to claim 2 comprising the step of flushing the sample reservoir after determining whether the initial portion of the sample meets one or more decision criteria.

8. The method according to claim 7 comprising the step of flushing the analytical instrument while the sample reservoir is being flushed.

9. The method according to claim 1 comprising the steps of:

(a) transferring the sample into a sample loop from a sampling probe, wherein the initial portion of the sample is transferred into the analytical instrument from the sample loop; and

(b) rinsing the sampling probe while the initial portion of the sample is being transferred into the analytical instrument.

10. The method according to claim 1 comprising the step of, in response to determining the initial portion of the sample to have failed to meet any of the one or more decision criteria, causing a solvent to flow into the analytical instrument.

11. The method according to claim 1 comprising the step of, in response to determining the initial portion of the sample to have failed to meet any of the one or more decision criteria, preventing a remaining portion of the sample from being injected into the analytical instrument.

12. The method according to claim 11 comprising the step of discarding the remaining portion of the sample.

13. The method according to claim 11 comprising the step of diverting the remaining portion of the sample away from the analytical instrument.

14. The method according to claim 13 comprising the step of transferring the remaining sample to an apparatus.

15. The method according to claim 14 wherein the apparatus is another analytical instrument.

16. The method according to claim 11 comprising the step of altering an analytical method performed by the analytical instrument.

17. A computer program product comprising computer-executable instructions embodied in a computer-readable medium for acquiring data from a sample, the steps comprising:

(a) causing at least an initial portion of a sample to be transferred into an analytical instrument;

(b) causing the analytical instrument to acquire data from the initial portion of the sample;

(c) while the analytical instrument is acquiring data, measuring one or more properties of the initial portion of the sample;

(d) determining whether the initial portion of the sample meets one or more decision criteria based on the one or more properties measured; and

(e) in response to determining the initial portion of the sample to have failed to meet any of the one or more decision criteria, causing the analytical instrument to cease acquiring data acquisition from the initial portion of the sample, or in response to determining the initial portion of the sample to have met all of the one or more decision criteria transferring an additional portion of the sample into the analytical instrument and causing the analytical instrument to acquire data from the additional portion.

18. The computer program product according to claim 17 wherein the initial portion of the sample is transferred into the analytical instrument from a sample reservoir.

19. The computer program product according to claim 18 comprising the step of, prior to transferring the initial portion of the sample into the analytical instrument, loading the sample into the sample reservoir from a sample conduit.

20. The computer program product according to claim 19 comprising the step of flushing the analytical instrument while the sample reservoir is being loaded.

21. The computer program product according to claim 19 comprising the step of flushing the sample conduit while the initial portion of the sample is being transferred into the analytical instrument.

22. The computer program product according to claim 21 wherein the sample conduit comprises a sampling probe.

23. The computer program product according to claim 18 comprising the step of flushing the sample reservoir after determining whether the initial portion of the sample meets one or more decision criteria.

24. The computer program product according to claim 23 comprising the step of flushing the analytical instrument while the sample reservoir is being flushed.

25. The computer program product according to claim 17 comprising the steps of:

(a) transferring the sample into a sample loop from a sampling probe, wherein the initial portion of the sample is transferred into the analytical instrument from the sample loop; and

(b) rinsing the sampling probe while the initial portion of the sample is being transferred into the analytical instrument.

26. The computer program product according to claim 17 comprising the step of, in response to determining the initial portion of the sample to have failed to meet any of the one or more decision criteria, causing a solvent to flow into the analytical instrument.

27. The computer program product according to claim 17 comprising the step of, in response to determining the initial portion of the sample to have failed to meet any of the one or more decision criteria, preventing a remaining portion of the sample from being injected into the analytical instrument.

28. The computer program product according to claim 27 comprising the step of discarding the remaining portion of the sample.

29. The computer program product according to claim 27 comprising the step of diverting the remaining portion of the sample away from the analytical instrument.

30. The computer program product according to claim 29 comprising the step of transferring the remaining sample to an apparatus.

31. The computer program product according to claim 30 wherein the apparatus is another analytical instrument.

32. The computer program product according to claim 27 comprising the step of altering an analytical method performed by the analytical instrument.

33. A method for acquiring data from a sample, comprising the steps of:

(a) loading a sample into a sample reservoir from a sample conduit;

(b) while the sample is being loaded, flushing an injection conduit;

(c) injecting at least a portion of the sample through the injection conduit into an analytical instrument;

(d) while the sample is being injected, flushing the sample conduit;

(e) flushing the sample reservoir;

(f) while the sample reservoir is being flushed, flushing the injection conduit; and

(g) repeating steps (a), (b), (c), and (d).

34. The method according to claim 33 comprising the steps of:

(a) providing a valve assembly in fluid communication with the sample reservoir, the sample conduit and the injection conduit;

(b) setting the valve assembly to a first position to enable the loading of the sample and the flushing of the injection conduit to occur simultaneously;

(c) setting the valve assembly to a second position to enable the injecting of the sample and the flushing of the sample conduit to occur simultaneously; and

(d) setting the valve assembly to a third position to enable the flushing of the sample and the flushing of the injection conduit to occur simultaneously.

35. A valve assembly for use in sample data acquisition, comprising:

(a) a sample loop; and

(b) a valve comprising an aspiration/dispensing port, a sampling port, a waste port, a pump-side port, and an instrument-side port, the valve being selectively adjustable to at least first, second and third positions, the first position defining a sample injection flow path and a sampling probe flushing path, the second position defining a sample loop loading flow path and an instrument flushing flow path, and the third position defining a sample loop flushing flow path.

36. The valve assembly according to claim 35 wherein:

(a) the sample injection flow path is directed from the pump-side injection port, through the sample loop, and to the instrument-side injection port;

(b) the sampling probe flushing path is directed from the aspiration/dispensing port to the sampling port;

(c) the sample loop loading flow path is directed from the sampling port to the sample loop;

(d) the instrument flushing flow path is directed from the pump-side injection port to the instrument-side injection port; and

(e) the sample loop flushing flow path is directed from the aspiration/dispensing port, through the sample loop, and to the waste port.

37. The valve assembly according to claim 36, wherein the sample loop comprises first and second openings, and the valve comprises a first sample loop port communicating with the first opening and a second sample loop port communicating with the second opening.

38. The valve assembly according to claim 36 comprising a valve structure and a movable valve body, wherein the valve structure comprises the aspiration/dispensing port, the sampling port, the waste port, the pump-side port, and the instrument-side port, and the valve body comprises a plurality of internal fluid passages selectively communicating with one or more of the ports of the valve structure at the first, second and third positions.

39. A valve assembly for use in sample data acquisition, comprising:
    (a) a sample loop;
    (b) a valve structure comprising an aspiration/dispensing port, a sampling port, a waste port, a pump-side port, and an instrument-side port;
    (c) a valve body selectively adjustable to at least first, second and third positions, wherein the first position defines a sample injection flow path and a sampling probe flushing path, the second position defines a sample loop loading flow path and an instrument flushing flow path, and the third position defines a sample loop flushing flow path.

40. The valve assembly according to claim 39 wherein:
    (a) the sample injection flow path is directed from the pump-side injection port, through the sample loop, and to the instrument-side injection port;
    (b) the sampling probe flushing path is directed from the aspiration/dispensing port to the sampling port;
    (c) the sample loop loading flow path is directed from the sampling port to the sample loop;
    (d) the instrument flushing flow path is directed from the pump-side injection port to the instrument-side injection port; and
    (e) the sample loop flushing flow path is directed from the aspiration/dispensing port, through the sample loop, and to the waste port.

41. The valve assembly according to claim 40, wherein the sample loop comprises first and second openings, and the valve structure comprises a first sample loop port communicating with the first opening and a second sample loop port communicating with the second opening.

42. The valve assembly according to claim 39 wherein the valve assembly has a dual-valve rotary configuration.

43. The valve assembly according to claim 39 wherein the valve assembly has a single-valve linear configuration.

44. The valve assembly according to claim 39 wherein the valve assembly has a single-valve rotary configuration.

45. A sample analysis system comprising:

(a) a robotic assembly;

(b) a sampling probe movably mounted to the robotic assembly;

(c) a sample loop; and

(d) a valve assembly mounted to the robotic assembly and comprising an aspiration/dispensing port, a sampling port, a waste port, a pump-side port, and an instrument-side port, the valve assembly being selectively adjustable to at least first, second and third positions, the first position defining a sample injection flow path and a sampling probe flushing path, the second position defining a sample loop loading flow path and an instrument flushing flow path, and the third position defining a sample loop flushing flow path.

46. The system according to claim 45 wherein:

(a) the sample injection flow path is directed from the pump-side injection port, through the sample loop, and to the instrument-side injection port;

(b) the sampling probe flushing path is directed from the aspiration/dispensing port, to the sampling port, and to the sampling probe;

(c) the sample loop loading flow path is directed from the sampling probe, to the sampling port, and to the sample loop;

(d) the instrument flushing flow path is directed from the pump-side injection port to the instrument-side injection port; and

(e) the sample loop flushing flow path is directed from the aspiration/dispensing port, through the sample loop, and to the waste port.

47. The system according to claim 45 comprising a reversible pump fluidly communicating with the aspiration/dispensing port.

48. The system according to claim 47 wherein the reversible pump is a syringe pump.

49. The system according to claim 45 comprising a waste receptacle fluidly communicating with the waste port.

50. The system according to claim 45 comprising an instrument pump fluidly communicating with the pump-side port.

51. The system according to claim 45 comprising an analytical instrument fluidly communicating with the instrument-side port.

52. The system according to claim 51 wherein the analytical instrument is a mass spectrometer.

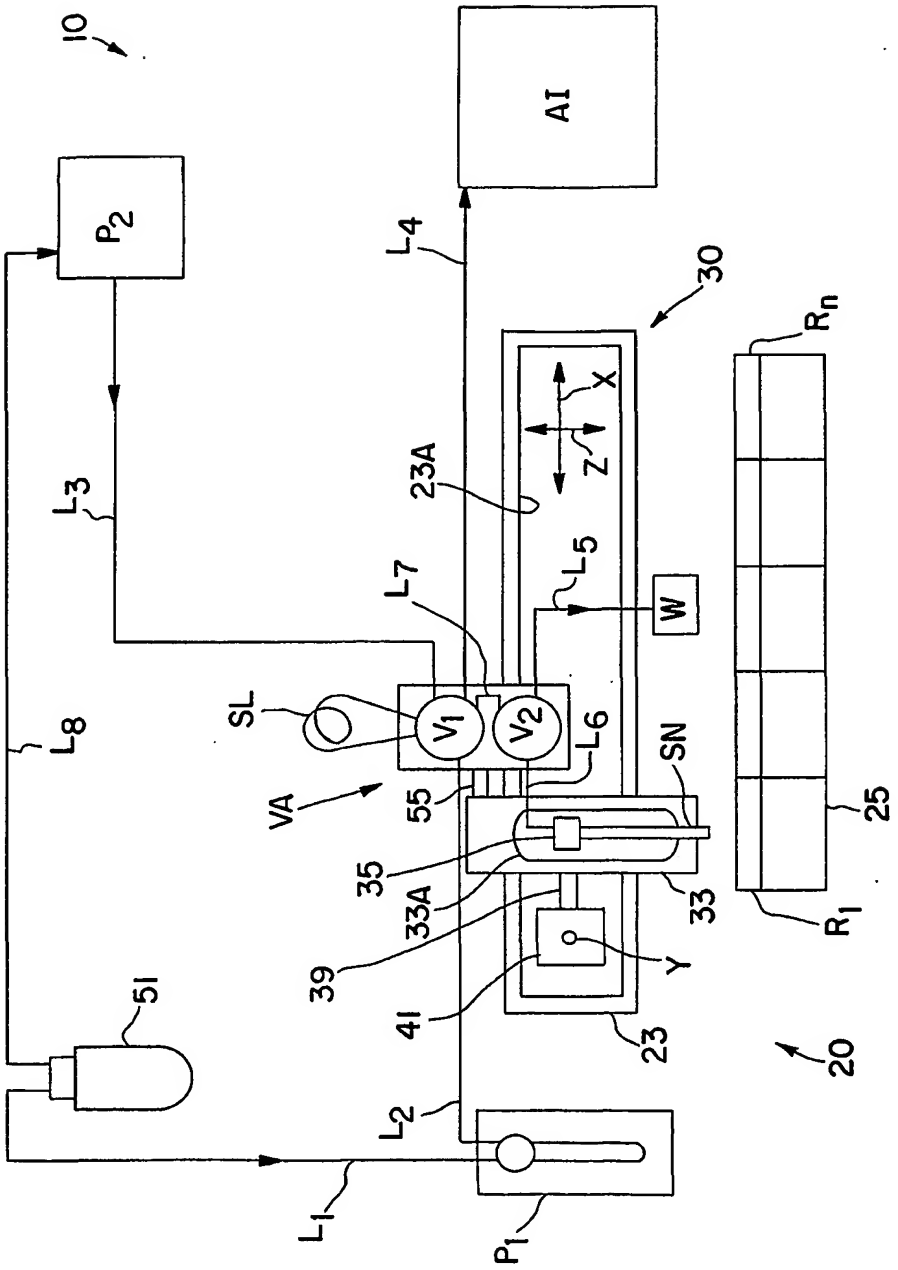

10
AI
P2
L4
30
Rn
X
Z
23A
L3
L5
W
L7
SL
V1
V2
L6
SN
L8
VA
55
25
35
33A
33
39
Y
R1
41
51
23
20
L2
L1
P1

FIG. 1

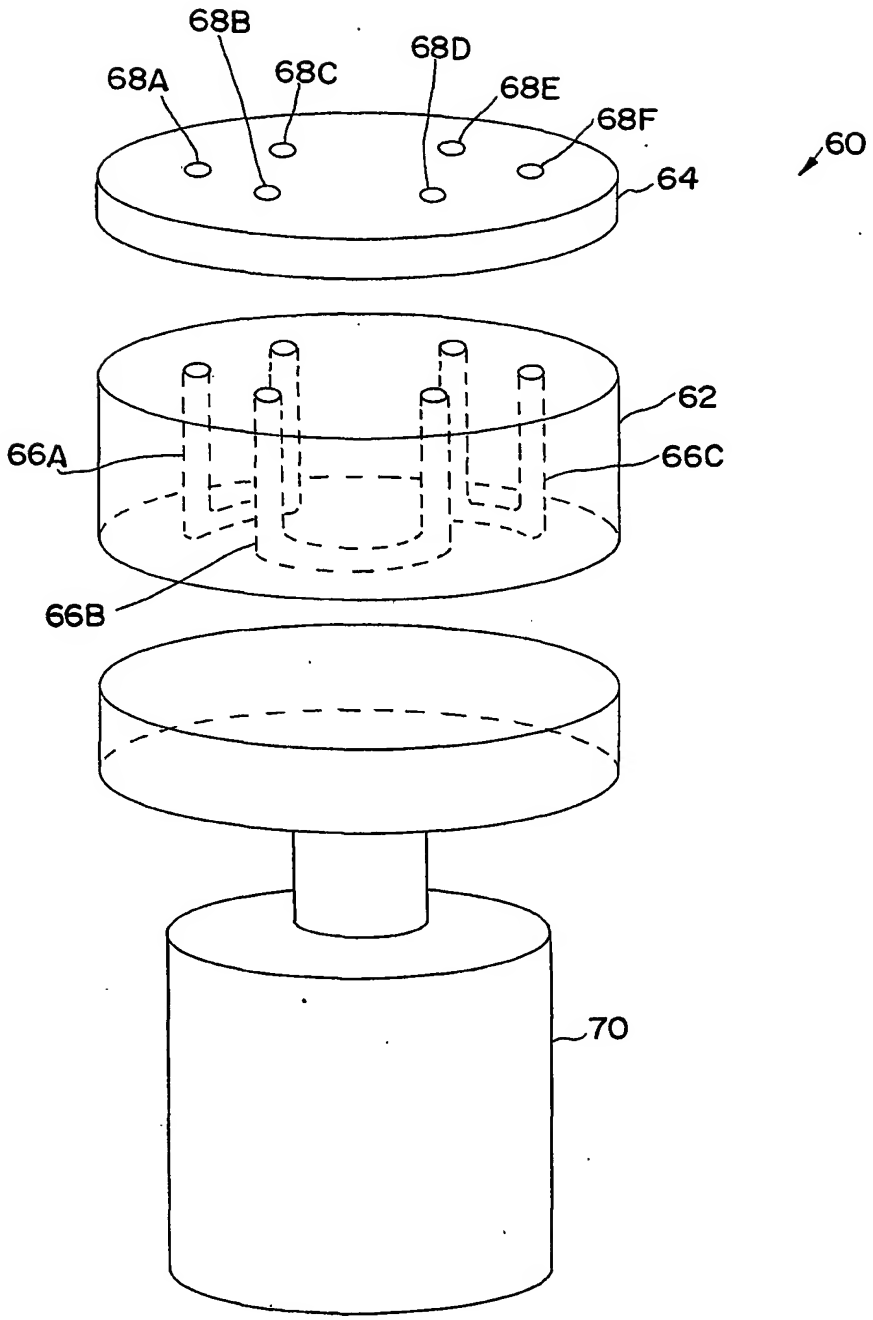


FIG. 2

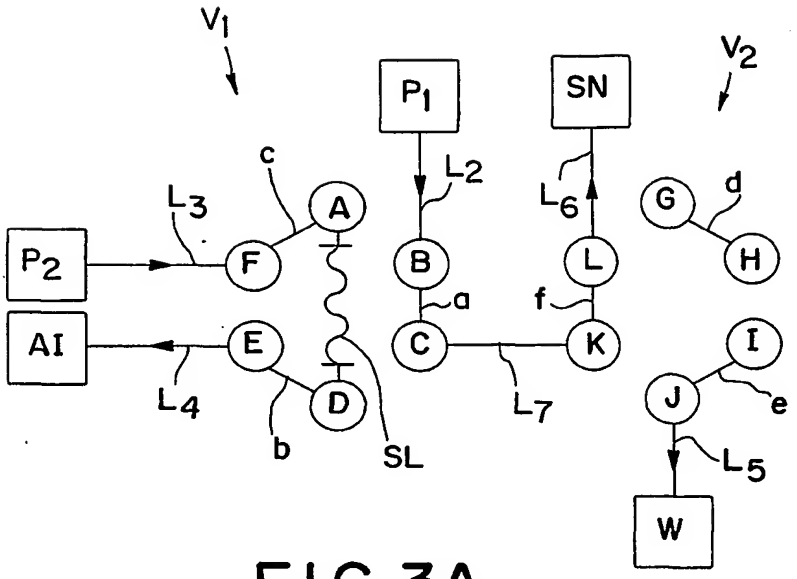

V1
P1
SN
V2
c
L2
L3
A
L6
G
d
P2
F
B
L
H
a
f
AI
E
C
K
I
L4
D
L7
J
e
b
SL
L5
W

FIG. 3A

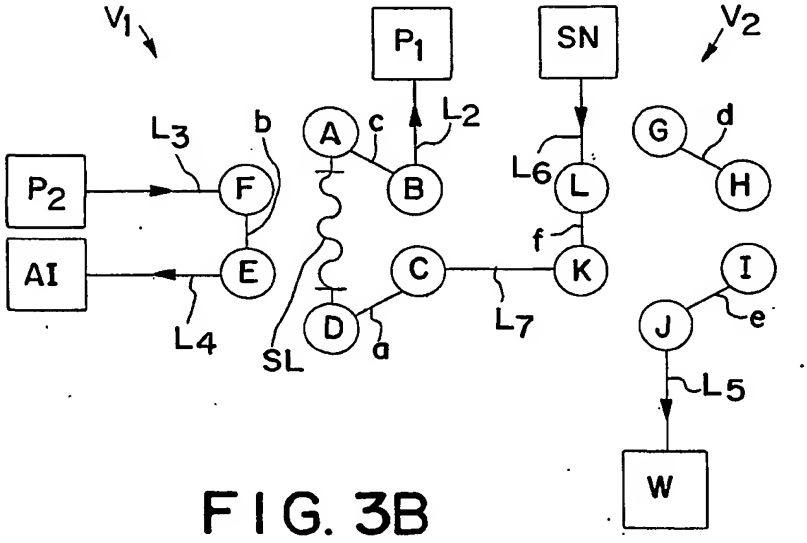

V1
P1
SN
V2
L3
b
A
c
L2
G
d
P2
F
B
L6
L
H
f
AI
E
C
K
I
L4
SL
D
a
L7
J
e
L5
W

FIG. 3B

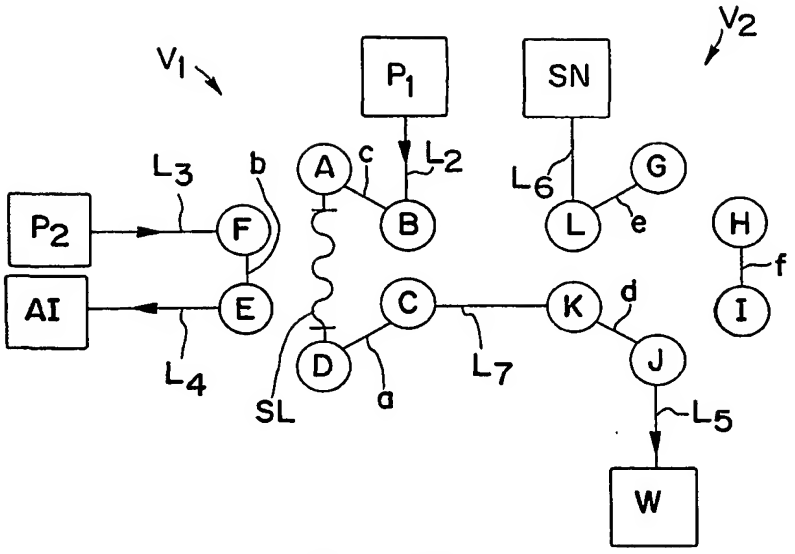

V1
V2
P1
SN
P2
AI
W
A
B
C
D
E
F
G
H
I
J
K
L
a
b
c
d
e
f
L2
L3
L4
L5
L6
L7
SL

FIG. 3C

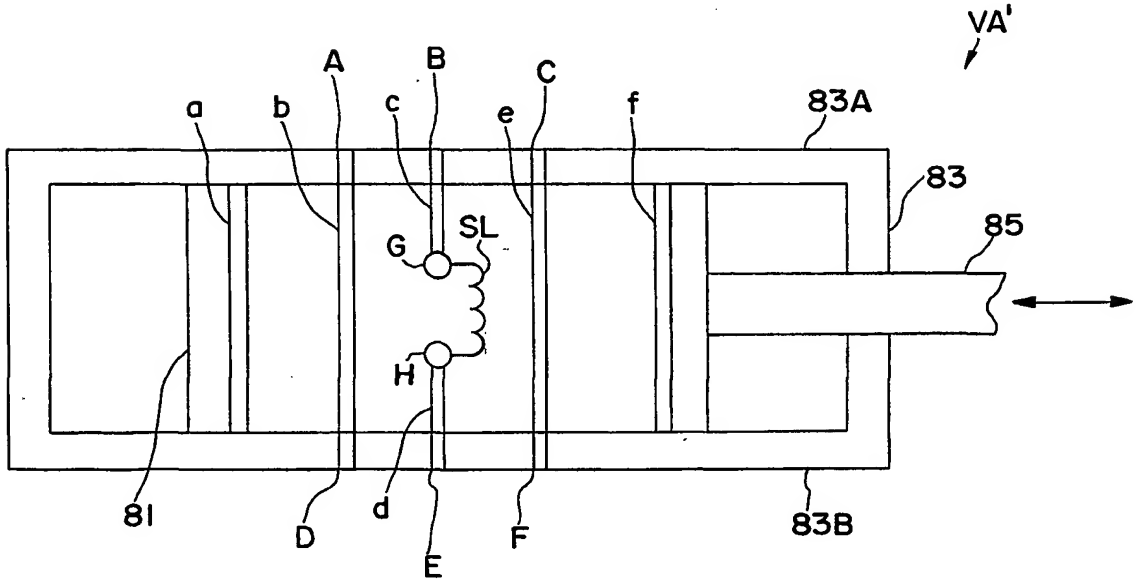

VA'
A
B
C
a
b
c
e
f
83A
83
85
SL
G
H
81
D
d
E
F
83B

FIG. 4

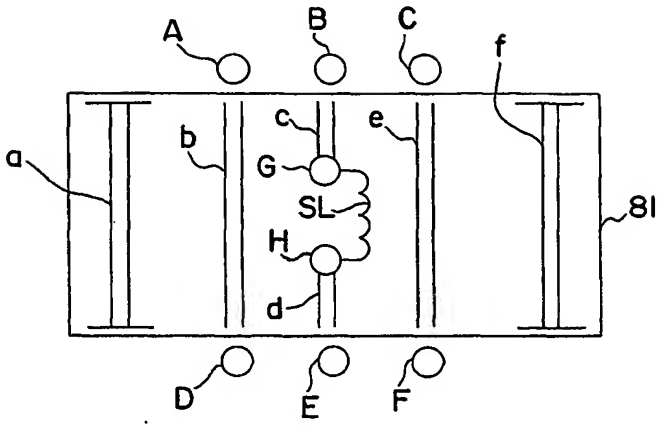


FIG. 5A

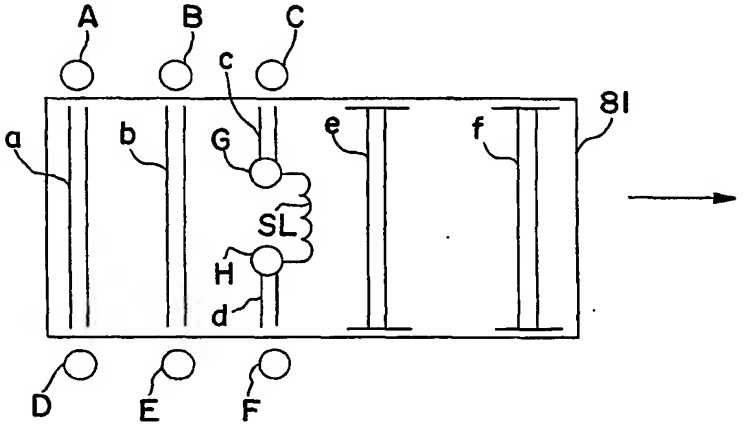


FIG. 5B

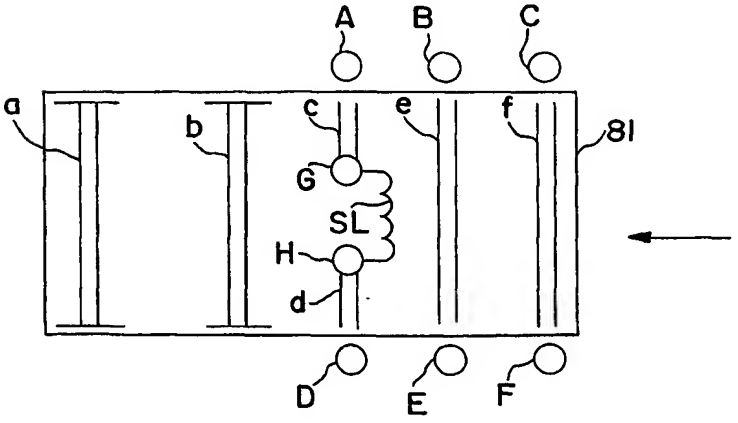


FIG. 5C

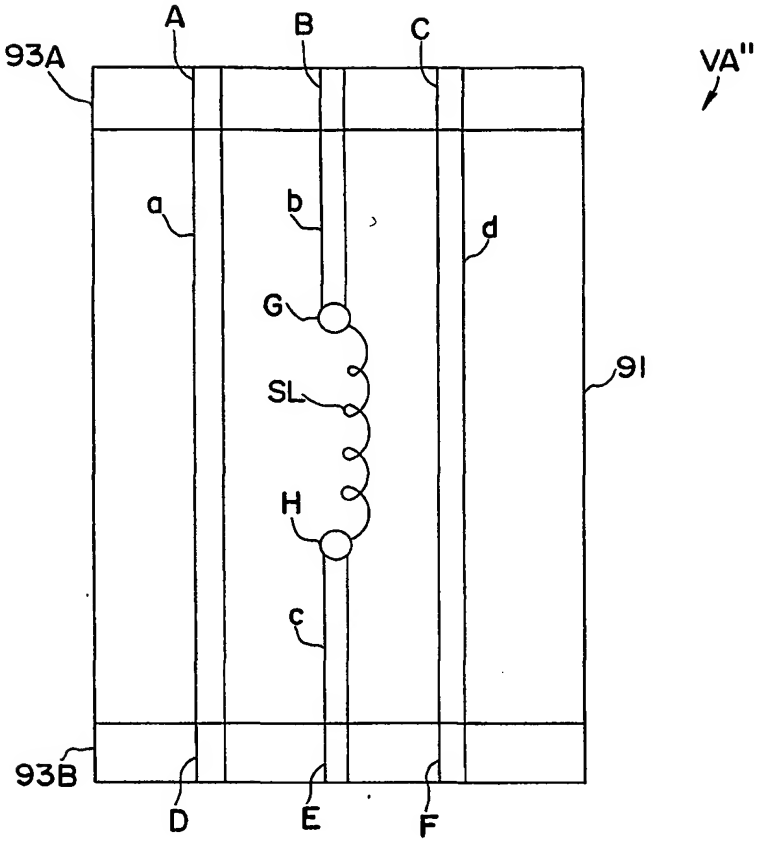


FIG. 6

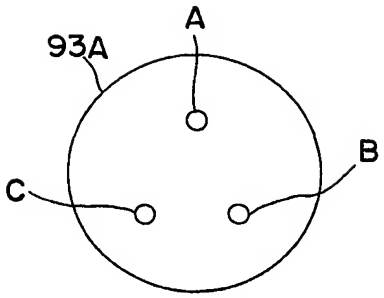


FIG. 7A

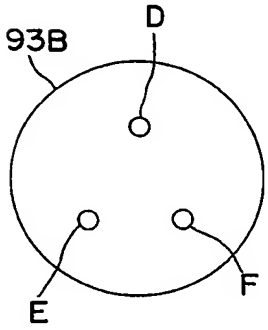


FIG. 7B

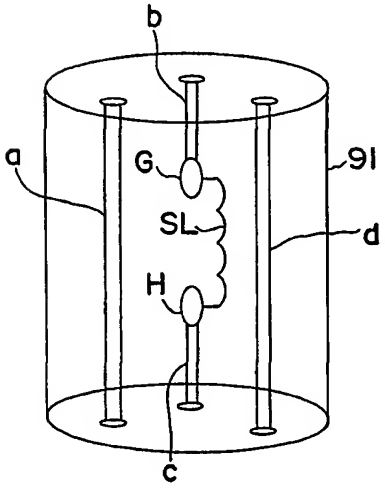


FIG. 7C

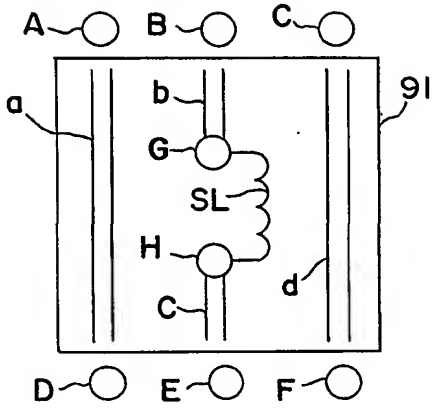


FIG. 8A

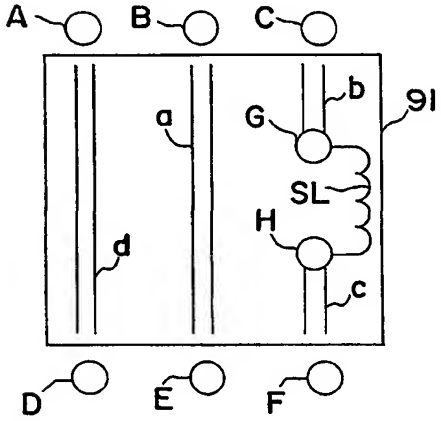


FIG. 8B

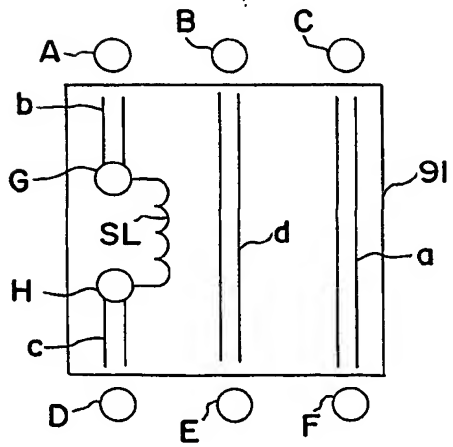


FIG. 8C

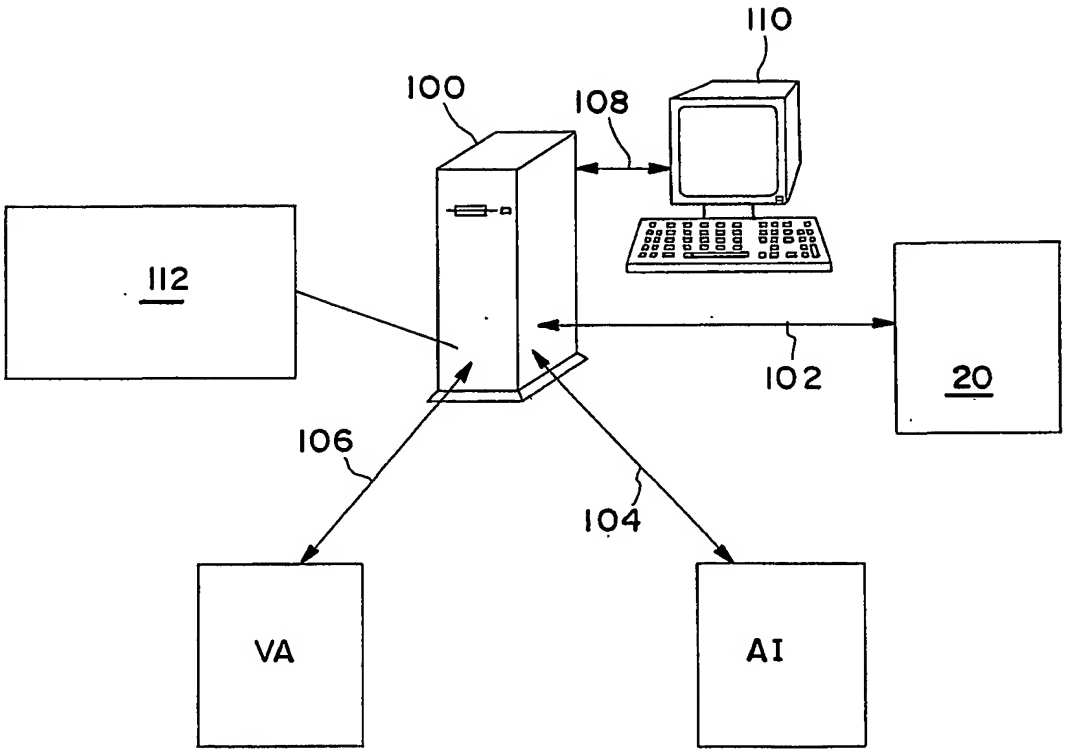


FIG. 9

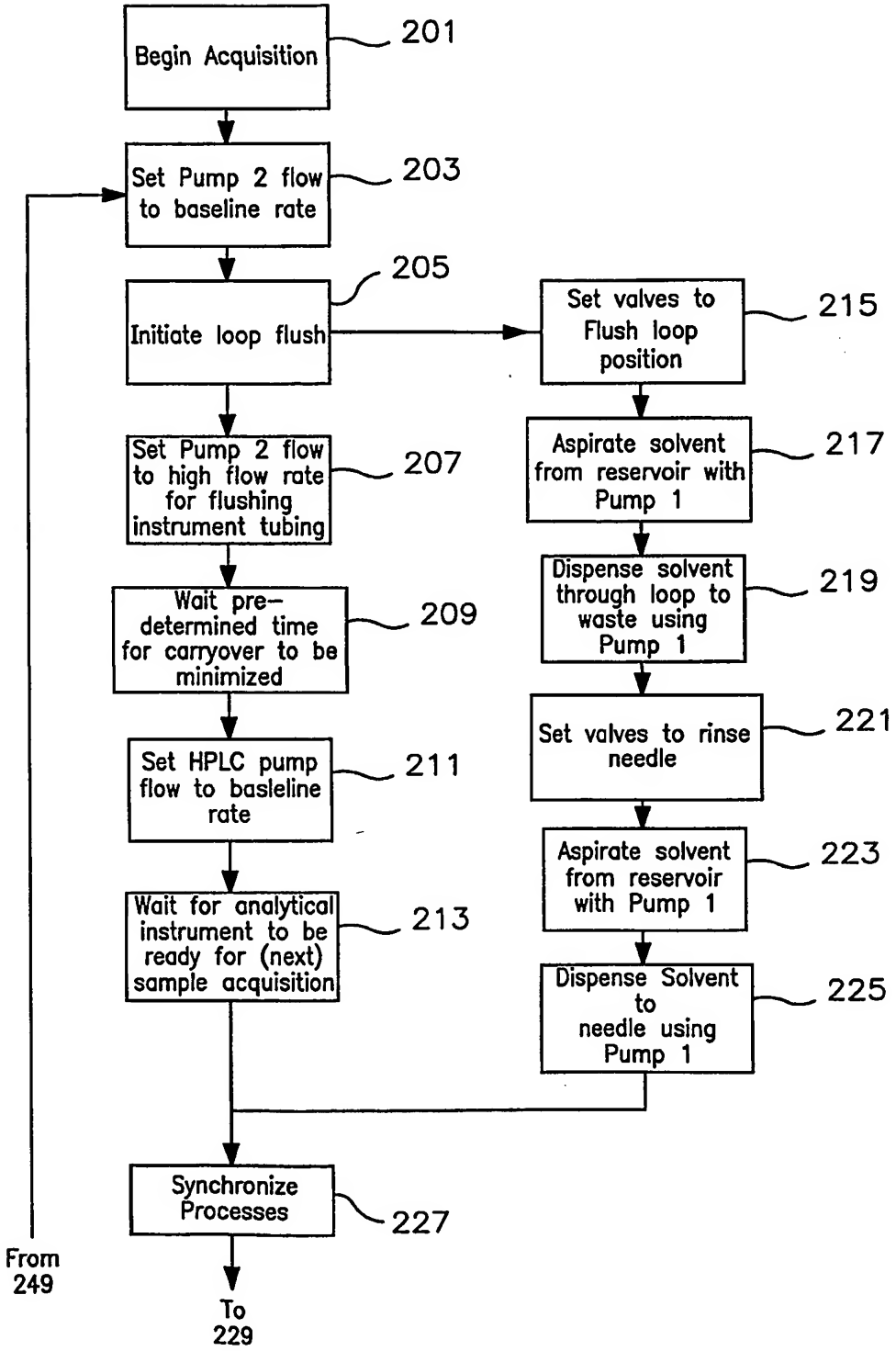

Begin Acquisition
201
Set Pump 2 flow to baseline rate
203
Initiate loop flush
205
Set valves to Flush loop position
215
Set Pump 2 flow to high flow rate for flushing instrument tubing
207
Aspirate solvent from reservoir with Pump 1
217
Wait pre-determined time for carryover to be minimized
209
Dispense solvent through loop to waste using Pump 1
219
Set HPLC pump flow to basleline rate
211
Set valves to rinse needle
221
Wait for analytical instrument to be ready for (next) sample acquisition
213
Aspirate solvent from reservoir with Pump 1
223
Dispense Solvent to needle using Pump 1
225
Synchronize Processes
227
From 249
To 229

FIG. 10A

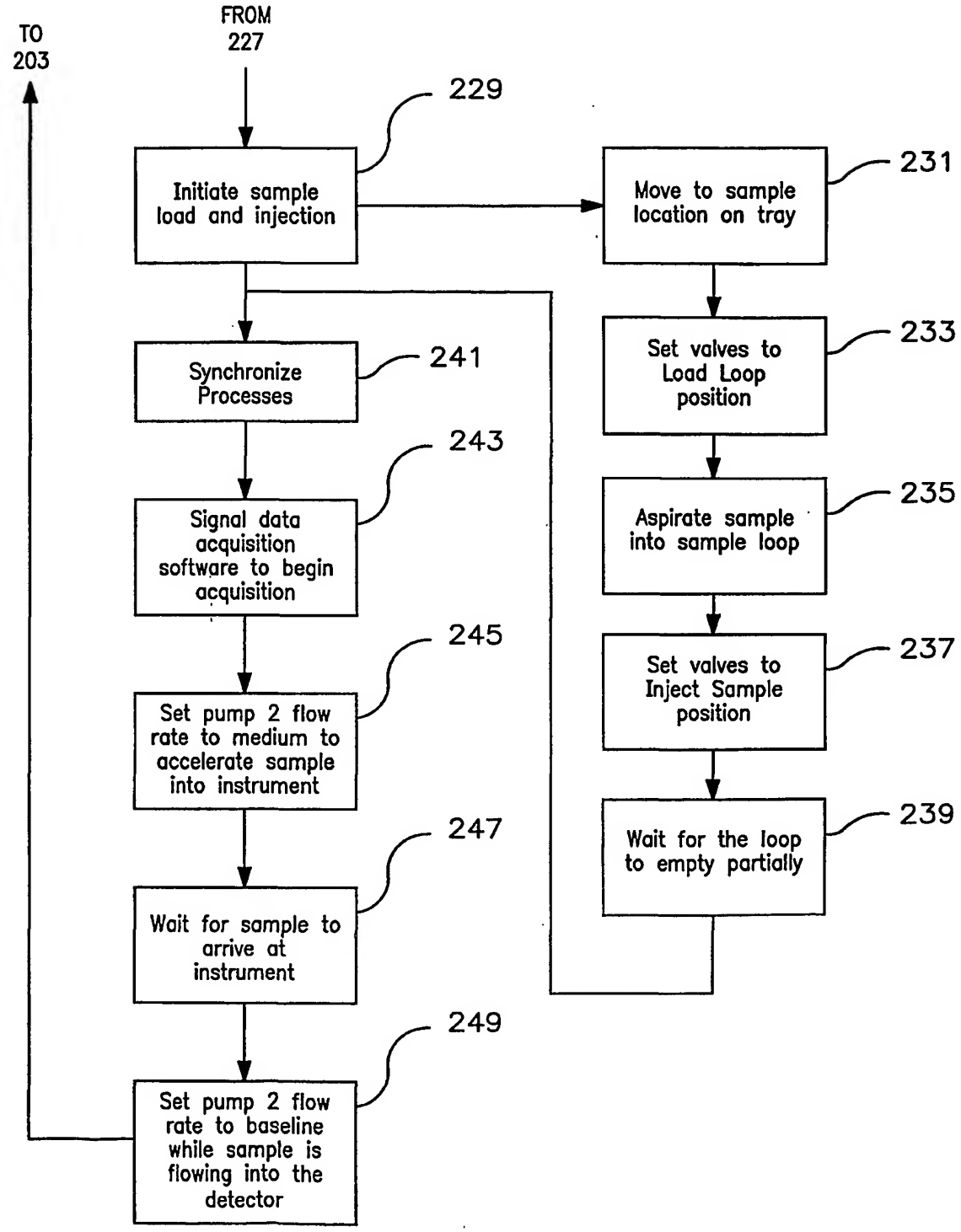

TO 203
FROM 227
229
Initiate sample load and injection
231
Move to sample location on tray
241
Synchronize Processes
233
Set valves to Load Loop position
243
Signal data acquisition software to begin acquisition
235
Aspirate sample into sample loop
245
Set pump 2 flow rate to medium to accelerate sample into instrument
237
Set valves to Inject Sample position
247
Wait for sample to arrive at instrument
239
Wait for the loop to empty partially
249
Set pump 2 flow rate to baseline while sample is flowing into the detector

FIG. 10B

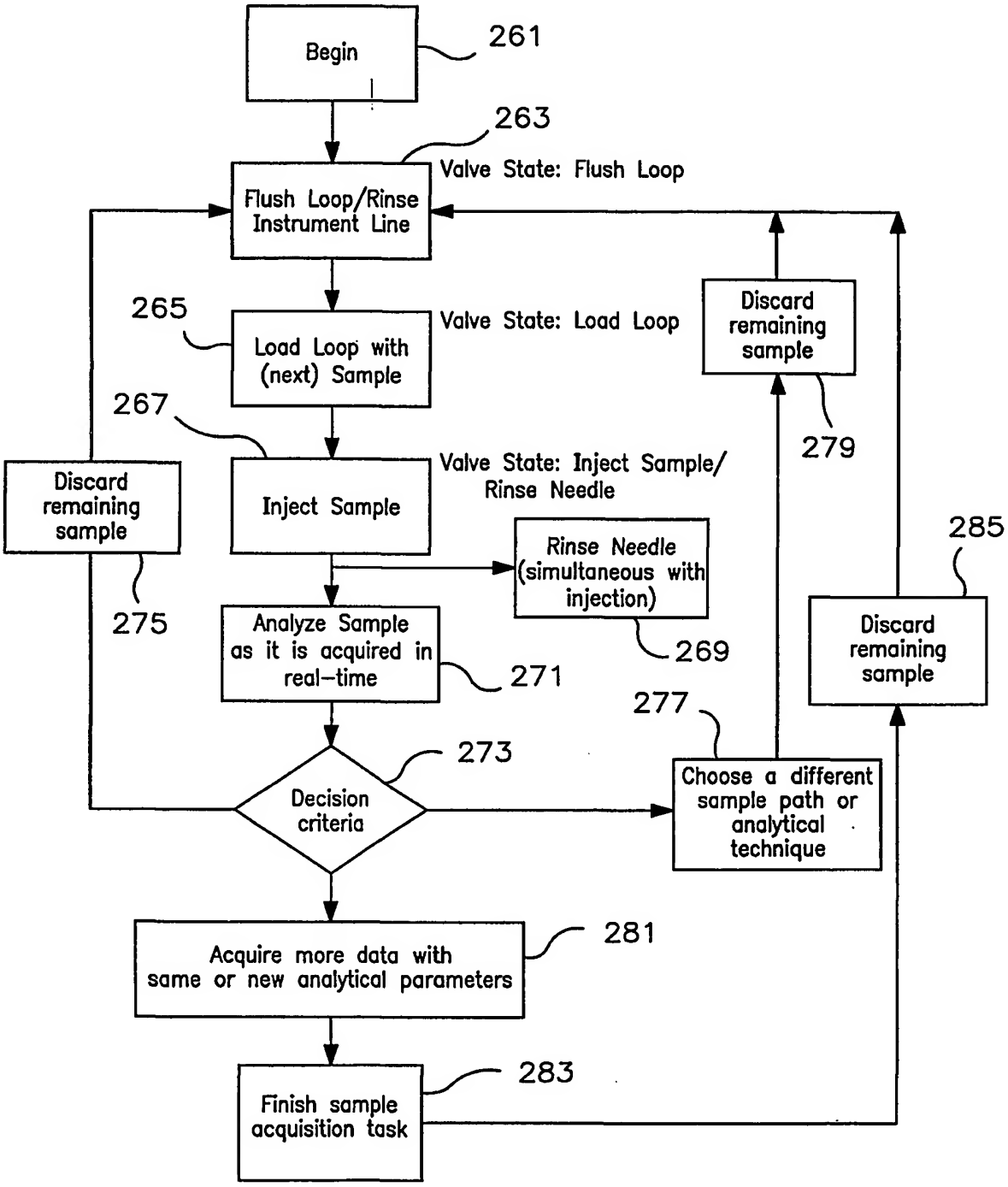

Begin
261
263
Valve State: Flush Loop
Flush Loop/Rinse Instrument Line
265
Load Loop with (next) Sample
Valve State: Load Loop
267
Inject Sample
Valve State: Inject Sample/ Rinse Needle
Discard remaining sample
275
Rinse Needle (simultaneous with injection)
269
Analyze Sample as it is acquired in real-time
271
Discard remaining sample
279
285
Discard remaining sample
277
273
Decision criteria
Choose a different sample path or analytical technique
Acquire more data with same or new analytical parameters
281
Finish sample acquisition task
283

FIG. 11

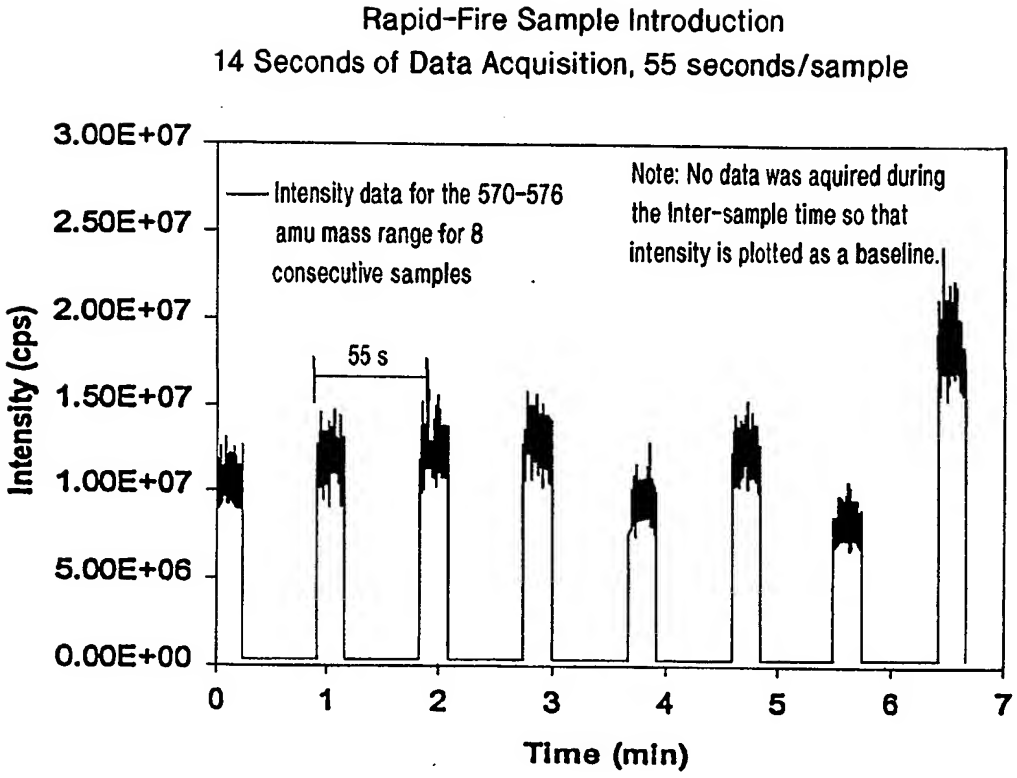

Rapid-Fire Sample Introduction
14 Seconds of Data Acquisition, 55 seconds/sample
3.00E+07
2.50E+07
2.00E+07
1.50E+07
1.00E+07
5.00E+06
0.00E+00
Intensity (cps)
Intensity data for the 570-576 amu mass range for 8 consecutive samples
Note: No data was aquired during the Inter-sample time so that intensity is plotted as a baseline.
55 s
0
1
2
3
4
5
6
7
Time (min)

FIG. 12

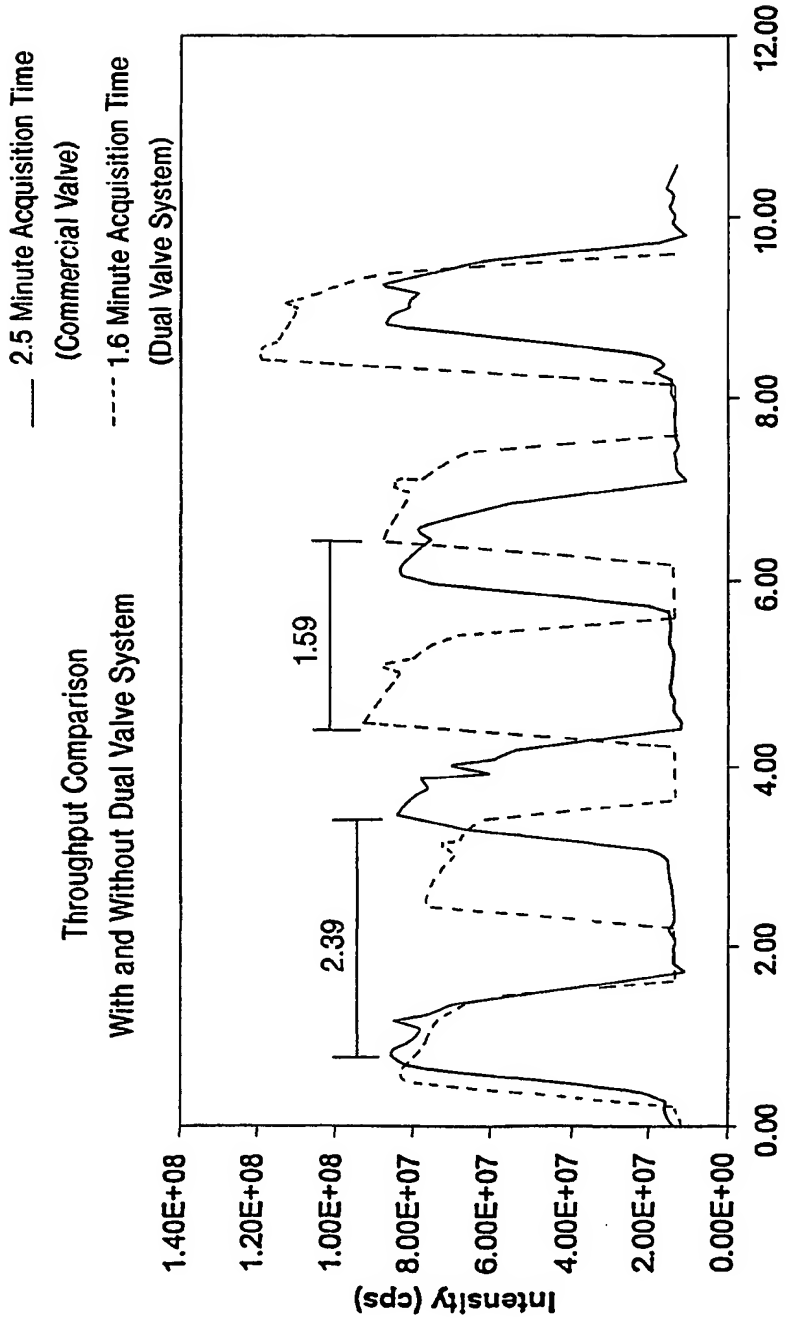

Throughput Comparison
With and Without Dual Valve System
2.5 Minute Acquisition Time
(Commercial Valve)
1.6 Minute Acquisition Time
(Dual Valve System)
2.39
1.59
Intensity (cps)
1.40E+08
1.20E+08
1.00E+08
8.00E+07
6.00E+07
4.00E+07
2.00E+07
0.00E+00
0.00
2.00
4.00
6.00
8.00
10.00
12.00
Time (min)

FIG. 13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/00064

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : G01N 35/02
US CL : 436/43, 48, 49, 55, 173, 180; 422/62, 63, 65, 82.05, 100, 103; 700/266; 702/22, 23, 30;
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 436/43, 48, 49, 55, 173, 180; 422/62, 63, 65, 82.05, 100, 103; 700/266; 702/22, 23, 30;

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,691,486 A (BEHRINGER et al) 25 November 1997 (25.11.1997), entire document.	1-41, 45-52 --- 42-43
X, P	US 6,143,573 A (RAO et al) 07 November 2000 (07.11.2000), entire document.	33-34, 45-52
X	US 5,297,431 A (WHITE) 29 March 1994 (29.03.1994), entire document.	33-41
X	US 5,624,846 A (HAYASHIBE et al) 29 April 1997 (29.04.1997), entire document.	1-32
A	US 5,633,168 A (GLASSCOCK et al) 27 May 1997 (27.05.1997), entire document.	1-52

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
14 May 2002 (14.05.2002)

Date of mailing of the international search report
[illegible] JUN 2002

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703)305-3230

Authorized officer
P. Kathryn Bex
Jean Proctor
Paralegal Specialist
Telephone No. 308-0661

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/00064

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.